
Supplement to:
Biological Psychiatry
Volume 83, Number 9S
May 1, 2018
Supplement: 73rd Annual Scientific Convention and Meeting
ISSN 0006-3223
www.sobp.org/journal
Official Journal of the Society of Biological Psychiatry

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Published since 1969

Aims and Scope

Biological Psychiatry is an official journal of the Society of Biological Psychiatry, whose purpose is to promote excellence in research investigating the nature, causes, mechanisms, and treatments of disorders of thought, emotion, and behavior. In accord with this mission, this peer-reviewed, rapid-publication, international journal publishes both basic and clinical contributions from all disciplines and research areas relevant to the pathophysiology and treatment of major psychiatric disorders.

Biological Psychiatry publishes novel results of original research that represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also published.

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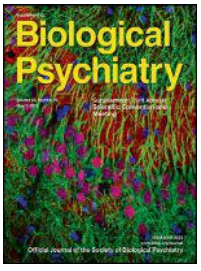
Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Volume 83, Number 9S, May 1, 2018

73RD Annual Scientific Convention and Meeting



The cover depicts neurons of the hippocampus activated by associative memory. Parra-Damas *et al.* visualized hippocampal neurons of an adult mouse with fluorescence microscopy using markers of dendrites (MAP2, green), nuclei (blue), and the transcriptional coactivator CRTC1 (red). See *Biol Psychiatry* (2017); 81:111–123. Image courtesy of Arnaldo Parra-Damas and Carlos A. Saura, Institut de Neurociències, Universitat Autònoma de Barcelona (Spain).

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Guide for Authors

Biological Psychiatry is the official journal of the Society of Biological Psychiatry. The *Journal* rapidly publishes reports of novel results on a broad range of topics related to the pathophysiology and treatment of major neuropsychiatric disorders. Both basic and clinical neuroscience contributions are encouraged, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches.

Except where explicitly stated otherwise, *Biological Psychiatry* conforms to the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE) (see Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (December 2017): Available from http://www.ICMJE.org).

All new manuscripts must be submitted through the journal website: https://www.editorialmanager.com/bps. All correspondence should be directed to the Editorial Office at Biol.Psych@utsouthwestern.edu.

ARTICLE TYPES

Archival Reports

Archival Reports are original research papers reporting novel results on a broad range of topics related to the pathophysiology and treatment of major neuropsychiatric disorders. Clear explication of methods and results is critical to facilitate review of papers and replicability of findings.

Word Limit: 4000 words in main body of text*
Abstract: 250 word limit; Structure as follows: Background, Methods, Results, Conclusions
Main Text: Structure as follows: Introduction, Methods and Materials, Results, Discussion
Tables/Figures: No limit, as needed
References: No limit, as needed
Supplement: Allowed, unlimited length

Priority Communications

These are Archival Reports that clearly document novel experimental findings of unusual and timely significance. These papers should represent a conceptual advance in the field and are not intended for publication of preliminary results. They are expected to be acceptable for publication in essentially the form submitted. Papers that require substantial revisions or do not fit the criteria will be considered as Archival Reports. See Archival Reports for structure, word length, and other requirements.

Reviews

Reviews are concise and focus on current aspects of interest and research. Reviews should be novel and have sufficient supporting literature, which should be integrated into a mechanistic model when applicable. Reviews should generally not focus solely on the authors' own work. All reviews must receive pre-approval from the Reviews Editor prior to submission, a process that is initiated via completion of a form available on our website; click here or see www.sobp.org/journal. Submit the completed form to Biol.Psych@utsouthwestern.edu, or contact the Editorial Office for further details regarding the pre-submission process for Reviews. Note that meta-analyses report original data and thus are not considered review papers; meta-analyses should be submitted as Archival Reports.

Word Limit: 4000 words in main body of text*
Abstract: 250 word limit; unstructured
Main Text: Structure with headings as needed
Tables/Figures: Allowed to summarize or illustrate important points
References: 150 maximum
Supplement: Allowed, unlimited length

Techniques and Methods
These articles feature new, improved, or noteworthy comments about techniques or methods relevant to basic or clinical research in, or treatment of, psychiatric disorders.

Word Limit: 3000 words in main body of text*
Abstract: 150 word limit; unstructured
Main Text: Structure as follows: Introduction, Methods and Materials, Results, Discussion
Tables/Figures: Maximum of two
References: No limit, as needed
Supplement: Allowed, unlimited length

Correspondence
These letters to the editor are directly related to methods, procedures or interpretation of data presented in work recently published in our journal and uses new analysis of data presented, the support of previously published work, and/or scientific points to be addressed based on methodological issues. They may also present a case report that clearly and unambiguously illustrates important new principles that have not yet been demonstrated in clinical trials. When warranted, a reply from author(s) of the original work is solicited; in such cases, the editor does not issue a final decision until both articles are submitted and the pair is then published together. Correspondence is published online only as e-content.

Word Limit: 1000 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured
Tables/Figures: Not encouraged, but 1-2 allowed if needed to illustrate important points
References: No limit, as needed
Supplement: Not permitted

Commentaries and Editorials
These articles address points directly related to articles in the concurrent issue, and/or focus on topics of current research and interest. These are generally invited, but interested contributors may contact the Editor.

Word Limit: 1500 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured, headings are not permitted
Tables/Figures: A single summarizing figure or table is encouraged
References: 10 maximum
Supplement: Not permitted

Early Career Investigator Commentaries
These articles provide publishing opportunities to early career investigators (ECI), as part of a joint project between the *Journal* and the Education Committee of the Society of Biological Psychiatry. These are invited articles for which an ECI serves as the sole and corresponding author. Each ECI shall be 1) a current member of the Society of Biological Psychiatry, 2) no more than 10 years out from terminal degree, and 3) not hold an academic faculty rank higher than Assistant Professor. A senior investigator mentors each ECI, acts as the content reviewer, and is recognized in the Acknowledgments section. ECI commentaries are published online only as e-content.

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Abstract: Not permitted
Main Text: Unstructured, headings are not permitted
Tables/Figures: A single summarizing figure or table is encouraged
References: 10 maximum
Supplement: Not permitted

Clinical Commentaries
These invited-only commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). Unlike regular commentaries, these articles have a specific clinical focus and are intended for a clinical audience, including medical students, residents, and clinicians. Clinical commentaries are published online only as e-content.

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*Word limits include main text of the article only, e.g., for Archival Reports, the word count includes the Introduction, Methods and Materials, Results, and Discussion sections. When calculating word counts, exclude abstract, references, table/figure legends, acknowledgments, and disclosures.

PREPARATION & FORMATTING REQUIREMENTS

The basic elements of all submissions are as follows:

- Cover letter
- Manuscript
  - Title page
  - Abstract
  - Main text of article
  - Acknowledgments
  - Disclosures
  - References
  - Legends for tables and figures
- Tables
- Figures
- Supplemental Information

Further details on each element are provided below, followed by guidance on style.

Cover Letter
Cover letters are optional for all submissions. A cover letter must be uploaded as a separate file, as it is not made available to peer reviewers.

Manuscript
Manuscripts should contain the following sections: title page, abstract, main article text, acknowledgments, disclosures, references, footnotes, and table/figure legends. The manuscript may also include tables, in text format, at the end of the file. Begin all sections on separate pages. The manuscript file should be supplied in Word, not in PDF.

Title Page
The title page should be the first page of the manuscript file and should include the following elements:

- Full article title, 200 characters or less; acronyms/abbreviations are prohibited
- Full names of all authors, in order, and their affiliations
- Corresponding author's complete mailing address, phone, and email
- Short/running title, 55 characters or less (including spaces); standard acronyms are permitted
- Six keywords
- Number of words in the abstract
- Number of words in the main text
- Number of figures, tables, and supplemental information, each listed separately; if zero, state zero

Abstract
Abstracts should be structured or unstructured according to the article type and should not exceed the word limits as detailed above. Structured abstracts should have the following sections: Background, Methods, Results, Conclusions. The Methods section should explicitly state the sample size and sex/species of subjects, when applicable. For those manuscripts that require clinical trials registration (see Clinical Trials Registration section, below), the registry name, URL, and registration number should be included at the end of the abstract. References are not permitted in abstracts. Avoid the use of abbreviations/acronyms that are not used at least three times.

Main Text
The text of papers should be double-spaced and structured according to the article type. It should not exceed the word limits as detailed above. Articles reporting original research (Archival Reports, Priority Communications, Techniques and Methods) should be structured with the following headings: Introduction, Methods and Materials, Results, Discussion. The introduction should provide a brief background and state the objectives/hypotheses of the current work; it should not include the findings/results of the study. The Methods and Materials section should include sufficient detail to allow other investigators to replicate the work. It is not appropriate to move the entire text of the methods to the supplement to adhere to the *Journal's* word count limits. Manufacturer name and location should be included at first mention, where applicable. Authors may reference other publications for methods that have previously been published in full detail elsewhere. Relevant ethics statements must be included; see Ethical Considerations section, below. The Results section should clearly present the experimental findings and test statistics in a logical order. The Discussion section should describe the results, interpret them in the context of prior literature, and discuss the implications and significance of the finding(s). Limitations of the current work should also be discussed.

Acknowledgments
This section should include detailed information regarding all sources of funding, including grant and other material or financial support. Specify granting agency, grant number, and recipient for each funding source. The role of study sponsor(s), if any, should be stated. Identify any data that was published previously, in abstract/poster form or on a preprint server. This section may also be used to acknowledge non-author contributors/collaborators and individuals who provided personal and technical assistance. If a consortium/group is listed as an author, then the individual members must be named here. Authors should secure written permission from all individuals named in this section.

GUIDE FOR AUTHORS

Disclosures

This section must include the required financial disclosures and conflict of interest statements for each author. Even if every author has nothing to disclose, this must be explicitly stated. See section on Disclosure, below.

References

References should be numbered and listed by their order of appearance in the text. Refer to references in the text with the appropriate number in parentheses. References in tables and figures should also be numbered. List all authors; if there are more than seven authors, list the first six then *et al.* Periodical abbreviations should follow those used by Index Medicus. It is not appropriate to reference papers that have not yet been published (i.e., are submitted or under review). The following are sample references for a published journal article (1), a book (2), and an edited book (3).

1. Krystal JH, Carter CS, Geschwind D, Manji HK, March JS, Nestler EJ, *et al.* (2008): It is time to take a stand for medical research and against terrorism targeting medical scientists. *Biol Psychiatry* 63: 725-727.
2. American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Publishing.
3. Martin JH (1985): Properties of cortical neurons, the EEG, and the mechanisms of epilepsy. In: Kandel ER, Schwartz JH, editors. *Principles of Neural Science, 2nd ed.* New York: Elsevier, pp 461-471.

The *Journal* also encourages the citation of underlying or relevant datasets in manuscripts by citing them in the text and including a data reference in the reference list. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so that it can be properly identified as a data reference. The [dataset] identifier does not appear in published articles.

Figure/Table Legends

Provide a brief title and legend for each figure and table. For multi-part figures, describe each panel. Avoid duplicating information in the figure/table legends that is already presented in the Methods and Materials or Results sections.

Tables

Tables should be cited in the text and numbered consecutively (i.e., 1, 2, 3) in the order of their mention. Each table should have a title, along with a brief description (legend). Do not duplicate information that is already presented in the text. Tables must be supplied in an editable format (Word or Excel). They may either be included at the end of the manuscript file, or uploaded individually, but not both. Table footnotes should use superscript lowercase letters, rather than symbols or bold/italic text. Colored text or shading is not permitted in tables.

Figures

Basic figure instructions are provided here. Further details regarding electronic artwork quality and preparation can be found at http://www.elsevier.com/artwork.

Key Requirements for Figures

File Formats	› TIFF, EPS, or PDF are preferred; JPEG is acceptable
Resolution	› Halftone or combination art: 300-500 dpi › Line art: 1000 dpi or supply as vector image
Image Size	› Single column width: 90 mm (255 pt) › 1.5 column width: 140 mm (397 pt) › Double column (full page) width: 190 mm (539 pt) › Note: 72 points = 1 inch
Font	› 8-12 point (minimum size variability) › Standard typeface (e.g., Arial, Times New Roman) › Consistent throughout
Multi-Panel Figures	› Label each panel/part with a capital letter (A, B, C,…)
Figure Titles/Legends	› Include in manuscript file, not in figure files
File Naming	› Use the figure number (Fig1.tif, Fig2.pdf, etc.)
Upload	› Supply as individual files (a single file for each figure)

Figures should be cited in the text, numbered consecutively (i.e., 1, 2, 3) in the order of their mention, and have brief legends. Each figure should be consistent in color, size, and font, and be designed proportionally so that it can later be sized as needed without loss of legibility or quality. Letters and numbers, in particular, should not vary greatly in size. RGB color mode is preferred over CMYK. High quality versions of each figure should be uploaded individually (i.e., two figures should be uploaded separately as Figure 1 and Figure 2). To reduce TIFF file size, flatten layers and then save with LZW compression before uploading. A minimum resolution of 300 dpi is required. Note that the quality of a low-resolution figure cannot be improved by artificially increasing the resolution in graphics software; figures must be initially created with sufficient quality/resolution. Figure titles and legends should be included as editable text in the manuscript file and not in the figure files.

Images should represent the original data and be minimally processed. Uniform adjustments (e.g., brightness, contrast) may be applied to an entire image, but individual elements of an image may not be adjusted, manipulated, or cropped in order to selectively highlight, obscure, delete, or otherwise misrepresent the image or its interpretation.

Color illustrations are accepted, although the cost of color printing must be paid by the author. Otherwise, all illustrations appear in color for the online version, but are reproduced in black and white in the print journal. Authors may supply black-and-white versions of color figures for printing purposes. Authors should be mindful of color choices that may be problematic when converted to gray-scale. The addition of textures and different line types helps avoid such problems.

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Supplemental information, relevant to the work but not critical to support the findings, is strongly encouraged by the *Journal* and is made available via links in the online article but not published in print. All such material is peer-reviewed, but not typeset or proofed and so should be carefully prepared. Unlike other files, all supplemental information (including text, tables, and figures) should be uploaded in a single Word file whenever possible. Exceptions are large and/or lengthy tables, which may be submitted in Excel. Word documents will automatically be converted to PDF before being posted online.

Do not number sections of text; rather, use textual headings to clearly differentiate sections. Supplementary figures and tables should appear with their titles/legends, and be numbered consecutively (i.e., Figure S1, Figure S2, Table S1). References should be included as a separate list from those in the main manuscript; number beginning with (1) and include a reference list at the end of the supplemental document. The CONSORT diagram for randomized controlled trials, when applicable, will be published in the supplement.

Multimedia Content

Multimedia content, in formats such as AVI or MPG, is encouraged and should be uploaded as an "e-component" in the drop-down menu at the upload screen.

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The *Journal* also encourages enrichment of online articles via support of 3D neuroimaging data visualizations. Authors may provide 3D neuroimaging data in either single (.nii) or dual (.hdr and .img) NIfTI file formats. Recommended size of a single uncompressed dataset is $\leq$100 MB. Multiple datasets can be submitted. Each dataset should be zipped and uploaded separately as "3D neuroimaging data" in the drop-down menu at the upload screen. Please provide a short informative description for each dataset by filling in the 'Description' field when uploading a dataset. If an article is accepted, the uploaded datasets will be available for download from the online article on ScienceDirect. For more information, see: http://www.elsevier.com/3DNeuroimaging.

Style

Basic style points are as follows:

Layout	› Double-space all text › Number each page › Line numbering is not necessary
Spelling	› Use American, as opposed to British, spellings
Language	› English
Font	› Any standard typeface is acceptable (e.g., Arial, Times New Roman) › Be consistent throughout (use the same typeface and size)
Acronyms/ Abbreviations	› Define at first use in the abstract › Define again at first use in the text and also in each legend › Avoid unnecessary/uncommon abbreviations
Nomenclature	› See below

Our readership is diverse, and authors should consider that many readers are in specialty areas other than their own. It is important, therefore, to avoid jargon. Manuscripts with the broadest appeal are focused and clearly written. In highly specialized areas, the introduction should be a concise primer.

We encourage authors whose first language is not English to ask a native English speaker to review their manuscript or to use a professional language editing service prior to submission. Accepted manuscripts are copyedited to conform to the *AMA Manual of Style*.

Psychopharmacology Nomenclature

Biological Psychiatry supports the Neuroscience-based Nomenclature (NbN) project (http://nbnomenclature.org/), which aims to promote the use of mechanism-based nomenclature that is pharmacologically-driven, rather than indication-based. The NbN system characterizes medications based on their pharmacological domain and mode(s) of action. Authors should use NbN's glossary or official apps in order to translate between the old and new nomenclature.

GUIDE FOR AUTHORS

Gene/Protein Nomenclature

Gene symbols should be italicized and differentiate by species. Human symbols should be all uppercase (*DISC1*), whereas symbols for rodents and other species should be lowercase using only an initial capital (*Disc1*). Protein products, regardless of species, are not italicized and use all uppercase letters (DISC1).

Authors should use approved nomenclature for gene symbols by consulting the appropriate public databases for correct gene names and symbols. Approved human gene symbols are available from HUGO Gene Nomenclature Committee (HGNC) at http://www.genenames.org/. Approved mouse symbols are provided by The Jackson Laboratory at http://www.informatics.jax.org/marker/. Use symbols (e.g., *SLC6A4, DISC1*) as opposed to italicized full names, and avoid listing multiple names separated by a slash, such as *'Oct4/Pou5f1'*. Use one name throughout and include any alias(es) upon the first reference. Authors should submit proposed gene names that are not already approved to the appropriate nomenclature committees as soon as possible. It is the authors' responsibility to ensure these are deposited and approved before publication of an article.

SUBMISSION PROCESS

All manuscripts must be submitted in electronic form through the *Biological Psychiatry* online submission and review website (https://www.editorialmanager.com/bps). Submission is a representation that all authors have personally reviewed and given final approval of the version submitted, and neither the manuscript nor its data have been previously published (except in abstract or preprint form) or are currently under consideration for publication elsewhere.

The *Journal* has created checklists to assist authors in the efficient submission of both new and revised manuscripts. They are entirely optional and intended solely to help authors adhere to our submission guidelines and save time so that submissions do not need to be returned for correction. The checklists are available here: http://www.biologicalpsychiatryjournal.com/content/bps-submission-checklists.

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The person designated in the system as the corresponding author must be one of the individuals named as a corresponding author on the title page. Upon finalizing the submission, the corresponding author will immediately receive an email notification that the submission has been received by the Editorial Office. If such documentation has not been received, then a problem has occurred during the submission process and should be investigated. Any manuscripts not conforming to these guidelines will be returned to the author for correction before the manuscript is processed. The manuscript status is available to the corresponding author at all times by logging into the website. The submission will receive a manuscript number once it has been processed and assigned to an editor.

New Submission

When submitting a new manuscript, authors will be asked to provide the following: valid email addresses for all authors; the names, emails and affiliations of 6 individuals who would be appropriate to review the work; and all submission files. Further details are as follows.

New Submission Files

To ease the burden of the submission process, we permit authors to upload the entire submission (minus a cover letter) as a single file, with pages numbered, in Word or PDF. Tables and figures may either be placed within the body of the manuscript or presented separately at the end. Authors must ensure that all elements are clearly legible for editors and peer reviewers. Alternatively, authors may upload individual files (cover letter, manuscript, figures, etc.) separately. All files should be labeled with appropriate and descriptive names (e.g., SmithText.doc, Fig1.eps, Table1.doc). The system will build a single PDF of the submission from the uploaded files. Regardless of how files are uploaded at this stage, all essential components of a manuscript are still required. See Manuscript section, above.

Author Notifications

The *Journal* sends a notification to every individual named as an author upon receipt of every new submission. This email provides details of the submission, including the full author list and the text of both the acknowledgments and disclosures sections. This policy requires valid email addresses for all coauthors, which must be supplied at submission; institutional email addresses are strongly preferred. When a consortium/group is named as an author, this group must be entered as an author at the Add/Edit/Remove Author screen. An email address for the primary contact/principal investigator of the consortium/group should be supplied. The named individual should be someone responsible for the consortium/group and must be a member of this group.

Referee Suggestions

For all new submissions (except Commentaries and Correspondence), authors are required to provide the full names and contact information (affiliation and email) of 6 individuals who are especially qualified to referee the work and would not have a conflict of interest in reviewing the manuscript. Affiliations of the suggested referees should all be different, and none should share an affiliation with any of the authors. Editors are not appropriate to suggest as a reviewer. Authors are also permitted to identify reviewers who should be excluded from reviewing their work, but final peer reviewer selections remain at the editors' discretion.

Revised Submission

Except for the additional guidelines noted here, requirements for revised submissions are the same as for new submissions. When submitting a revised manuscript, authors are asked to provide a detailed response to reviewers, which must be uploaded as a unique Word or PDF file (separate from the cover letter). Authors may upload a 'tracked changes' version of their revision, but must always include a 'clean' non-marked version of the manuscript. If revisions are a condition of publication, only two revised versions of the paper will be considered. Unsolicited revisions are not allowed.

Revised Submission Files

All files (cover letter, response to reviewers, manuscript, figures, etc.) must be uploaded separately at revision, and should be labeled with appropriate and descriptive file names (e.g., SmithText.doc, Fig1.tif, Table1.doc). File format requirements are specified in the below table. The system will build a single PDF of the submission from the uploaded files. Authors should be careful to replace all files that have been updated since original submission and ensure all files are correctly labeled (particularly if figures and/or tables have been rearranged and subsequently renumbered). On the title page, update word, figure, and table counts as necessary.

File Type Requirements

Cover Letter	Word or PDF
Detailed Response to Reviewers	Word or PDF
Manuscript	Word
Tables	Word or Excel
Figures	TIFF, EPS, or PDF
Supplement	Word

Word Limits

Biological Psychiatry strictly enforces its word limits when a revised manuscript is submitted. Needing to address the reviewers' concerns is not a sufficient reason for exceeding the stated maximum word limits. We advise authors to critically evaluate their manuscripts to ensure that they are written as concisely and clearly as possible. Additionally, the *Journal* strongly encourages the use of Supplemental Information. This can be text, tables, and/or figures that are relevant to the work but not critical to support the findings. Supplemental Information is published online, but does not appear in print and therefore does not count against the word limits.

In This Issue Feature

The submission of revised manuscripts (except Commentaries and Correspondence) requires a new unique file with a brief non-technical summary of the article. The blurb should be uploaded as a text file, 50-75 words in length, and be written in laymen's terms. Should the article be accepted for publication, this summary will be used for the *In This Issue* feature when the article is published.

PEER REVIEW PROCESS

All submissions (with the general exception of Editorials, Commentaries, and Correspondence) will be subject to blinded peer review. The actual selection of reviewers will be made by the editors. As a general rule, papers will be evaluated by three or more independent reviewers and, on occasion, an additional review for statistical adequacy may also be obtained. The comments of the reviewers are generally communicated to the authors within 30-45 days of submission.

Biological Psychiatry excludes reviewers who work at the same institution as any author, or those who have any other obvious conflict of interest. The identity of individual reviewers remains confidential to all parties except the Editorial Office. Reviewers are expected to treat manuscripts under peer review with the strictest confidentiality.

GUIDE FOR AUTHORS

Authors should be aware that manuscripts may be returned without outside review when the editors deem that the paper is of insufficient general interest for the broad readership of *Biological Psychiatry*, or that the scientific priority is such that it is unlikely to receive favorable reviews. Editorial rejection is done to speed up the editorial process and to allow the authors' papers to be promptly submitted and reviewed elsewhere.

Biological Psychiatry is a member of the Neuroscience Peer Review Consortium, an alliance of neuroscience journals that have agreed to accept manuscript reviews from each other. Authors may submit a revision of their manuscript to another Consortium journal, and, at the author's request, *Biological Psychiatry* will forward the peer reviews to that journal. Authors can find a list of Consortium journals and details about forwarding reviews at http://nprc.incf.org.

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Updated 2/6/18

Biological Psychiatry

Welcome

We are very pleased to welcome you to the 2018 Annual Meeting of the Society of Biological Psychiatry. It is a special pleasure to hold the meeting in New York City. The meeting theme this year, **Biomarkers, Biomodels, and Psychiatric Disorders,** represents the timely sentiment among many brain biologists to use the approaches and tools of modern neuroscience to identify neural mechanisms in psychiatric disorders. It is a task that falls to groups like SOBP and, as discovery comes, will bring untold benefit to the disorders that plague our patients, families, and friends.

The scientific submissions to the 2018 annual meeting seemed like a landslide: we have 13 plenary speakers; 63 symposia will be available, as will 48 oral sessions, 853 posters, and over 300 late-breaking abstract presentations. The Program Committee had a busy season and brought order and clarity to the organization of the 135 symposia and over 1300 abstracts submitted in 2018. The 2018 SOBP meeting will feature striking new areas of science, broadly spread throughout the 3-day meeting, including discovery neuroscience, study follow-ups, and data reports, as well as insightful formulations around brain mechanisms of psychiatric conditions. Our attendees will be varied, from clinicians, full-time scientists, and science and medicine educators, to young people training in the field. Industrial, academic, and government scientists have the opportunity to gather at SOBP, bound by a common passion for understanding the brain and seeing new knowledge applied to mechanisms of psychiatric disorders with the development of new treatments. Like last year's meeting, this year's meeting is flanked by the American Psychiatric Association Meeting, marking our last paired meeting with the APA. Also, we have forged a collaboration with the Computational Psychiatry consortium and feature their Computational Psychiatry Symposium as a pre-satellite to the SOBP Annual Meeting.

This year, we say good-bye to our long-time SOBP organizers, Maggie Peterson and Mimi Macke, and welcome our new group, Parthenon Management Group, as our full-time team. There is good to say on all sides, with volumes of thanks to Maggie and Mimi and a wondrous welcome to PMG and John White.

We welcome you to the 2018 Annual Meeting of the Society of Biological Psychiatry to participate, network, learn, and share.

Carol A. Tamminga, M.D.
SOBP President

Lori McMahon, Ph.D.
SOBP Program Committee Chair

 ISSN: 0006-3223

Plenary and Symposium Abstracts

Thursday, May 10, 2018

PLENARY
Emerging Mechanisms & Biomarkers
8:00 a.m. - 11:30 a.m.
Chair: Lori McMahon

1. Sex Differences in the Molecular Basis of Depression

Eric Nestler

Mount Sinai School of Medicine

Depression is a common, chronic, and debilitating syndrome. Although many patients benefit from antidepressant medications or other therapies, only about half of depressed patients show a complete remission, which underscores the need for more effective agents. The mechanisms that precipitate depression, such as stress, are incompletely understood. One mystery of the disease is its long-lasting nature and delayed response to antidepressant treatment. This persistence is thought to be mediated by slowly developing but stable adaptations in the brain, which might include regulation of gene expression and chromatin structure.

We are using several chronic stress models in mice as well as analysis of human postmortem brain tissue at autopsy, in combination with RNA-sequencing and other genome-wide approaches, to identify changes in gene expression, and associated changes in chromatin regulation, associated with depression or antidepressant treatment. We also study resilience by analyzing mice that maintain normal functioning despite exposure to severe stress. We take a circuit-wide approach by analyzing these molecular endpoints in several limbic brain regions implicated in depression. One major focus of these investigations are dramatic sex differences seen across these brain regions between depressed men and women, a finding recapitulated in stressed male and female mice. Another major focus is how gene expression and chromatin structure are altered in response to stress early in life, which then increases the susceptibility of individuals to subsequent stress for a lifetime.

Together, this work is providing novel insight into the molecular mechanisms underlying depression and other stress-related disorders. The findings also suggest novel leads for the development of new antidepressant treatments. For example, our findings on resilience suggest the novel approach of developing medications that promote resilience and not just those that oppose the deleterious effects of stress.

Keywords: Depression, Antidepressant Response, Resilience, Gene Expression, Chromatin

2. Molecular Architecture of the Circadian Clock in Mammals

Joseph Takahashi

Howard Hughes Medical Institute, University of Texas Southwestern Medical Center

The molecular mechanism of circadian clocks in mammals is generated by a set of genes forming a transcriptional autoregulatory feedback loop. The “core clock genes” include: Clock, Bmal1, Per1, Per2, Cry1 and Cry2. The discovery of “clock genes” led to the realization that circadian gene expression is widespread throughout the body and that the clock is cell autonomous. The cellular autonomy of circadian clocks has raised a number of questions concerning synchronization and coherence of rhythms at the cellular level as well as circadian organization at the systems level. The role of clocks in peripheral tissues has a number of important implications for disease.

In the circadian clock mechanism, CLOCK and BMAL1 activate the transcription of the Period and Cryptochrome genes. The PERIOD and CRYPTOCHROME proteins then feedback and repress their own transcription by interaction with CLOCK and BMAL1. In the mouse liver, CLOCK and BMAL1 interact with the regulatory regions of thousands of genes, which are both cyclically and constitutively expressed. These target genes are highly enriched for metabolic pathways and indeed all fundamental metabolic pathways in the cell are direct targets of CLOCK:BMAL1. Circadian transcription in the liver is clustered in time and this is accompanied by circadian occupancy of RNA polymerase II recruitment and initiation. These changes also lead to circadian fluctuations in histone H3 lysine4 trimethylation (H3K4me3) as well as H3 lysine9 acetylation (H3K9ac) and H3 lysine27 acetylation (H3K27ac). Thus, the circadian clock regulates global transcriptional poise and chromatin state by regulation of RNA polymerase II. A mechanistic description of the core circadian clock mechanism should promote our understanding of how the circadian clock system influences behavior, physiology and cellular and molecular function as well as disease mechanisms underlying metabolism, cancer, immunology and neurodegenerative and psychiatric disorders.

Keywords: Circadian Rhythms, Clock Genes, Transcription Regulation, Chromatin

3. Decoding Distinct Stress States From Brain-Wide Spatiotemporal Dynamics

Kafui Dzirasa

Duke University Medical Center

ISSN: 0006-3223

Fluctuations in brain-wide local field potential oscillations reflect emergent network-level signals that mediate behavior. Cracking the code whereby these oscillations coordinate in time and space (spatiotemporal dynamics) to represent complex behaviors would provide fundamental insights into how the brain signals emotional pathology. Using machine learning, we discover a spatiotemporal dynamic network that predicts the emergence of depression-related behavioral dysfunction in mice subjected to chronic social defeat stress. Activity in this network originates in prefrontal cortex and ventral striatum, relays through amygdala and ventral tegmental area, and converges in ventral hippocampus. This network is increased by acute threat, and it is also enhanced in three independent models of depression vulnerability. Finally, we demonstrate that this vulnerability network is biologically distinct from the networks that encode dysfunction after stress. Thus, these findings reveal a convergent mechanism through which depression vulnerability is mediated in the brain.
Keywords: Resilience, Vulnerable

4. Oscillations in Brain Networks as Therapeutic Targets: Identification, Engagement, and Validation

Flavio Frohlich

UNC - Chapel Hill

Originally, the rhythmic structure of brain activity was dismissed as a meaningless side product of neuronal activity. More recently, it has become increasingly clear that rhythmic signals generated by brain networks play an important causal role in cognition and behavior. These network oscillations exhibit relatively specific deficits in psychiatric disorders. This plenary talk will show how the advent of non-invasive brain stimulation for modulating cortical oscillations has provided groundbreaking insights into the causal role of oscillations in physiological and pathological brain function. The confluence of engineering, biology, and medicine has recently enabled the rational design of the next generation of therapeutic strategies that target these network oscillations for the treatment of psychiatric disorders such as depression and schizophrenia. The talk will conclude with an outlook into the future what psychiatry enabled by network neuroscience may look like.
Keywords: Brain Networks, Oscillations, Noninvasive Brain Stimulation

SYMPOSIUM
Mood Instability: Measurement, Meaning and Mechanisms
12:30 p.m. - 2:30 p.m.
Chair: Paul Harrison

5. Mood Instability: A Systematic Review of Definitions and Measures, and its Epidemiology and Clinical Correlates

Matthew Broome[1] and Steven Marwaha[2]

[1]University of Birmingham, [2]University of Warwick

Background: Literature offers a variety of definitions and conceptualisations of mood instability, and in turn, many tools to measure it. Our initial research was to conduct a systematic review synthesising conceptions and measures of mood instability in clinical populations. In parallel, we began examining prevalence and clinical correlates of mood instability in a UK household morbidity survey, to determine whether mood instability had a clinical impact over and above the psychiatric diagnoses also present in the population.
Methods: Systematic review/evidence synthesis
Epidemiology/secondary data analysis
Results: The systematic review found three core attributes of mood instability. We propose that mood instability is defined as "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences". In our epidemiological work (n=7403) we found a prevalence of mood instability of 13.9%, and that it was associated with health service use and suicidal ideation. Longitudinally, mood instability may mediate some of the risk of childhood trauma causing psychosis.
Conclusions: Our work offers a definition of mood instability synthesising conceptions from the literature, and suggesting measures that can be used in research to capture the three attributes of the construct. The epidemiological project demonstrates that mood instability is prevalent and cuts across psychiatric diagnoses. Further, it is clinically important as indexes outcomes such as health service use and suicidal ideation, beyond that associated with any psychiatric diagnoses present. Lastly, mood instability may also have an important role in the aetiology of mental disorders and may serve as a target for future intervention strategies.
Supported By: English Department of Health, the Scottish Executive, the National Assembly for Wales, NHS Information Centre for Health and Social Care
Keywords: Mood Instability, Affective Instability, Epidemiology, Systematic Review, Transdiagnostic

6. Genome-Wide Associations With Mood Instability in the UK Biobank Cohort

Daniel Smith[1]

[1]University of Glasgow

Background: Mood instability is a core clinical feature of affective and psychotic disorders and may be a useful phenotype for identifying biology that cuts across psychiatric categories.
Methods: We recently completed a genome-wide association study (GWAS) of mood instability within the first genetic data release of UK Biobank participants (53,525 cases and 60,443 controls).
Results: This GWAS identified four independently-associated loci (on chromosomes eight, nine, 14 and 18), and a common single nucleotide polymorphism (SNP)-based heritability estimate of approximately 8% (Ward et al, Translational Psychiatry, in press). Although mood instability was previously suspected to be a partially heritable trait, prior evidence of this was inconclusive. This study also found a strong genetic correlation between mood instability and major depressive

disorder and a small but significant genetic correlation with both schizophrenia and anxiety disorders. Several genes at the associated loci may have a role in regulating mood. We are working on a larger GWAS of mood instability which makes use of the full genetic data release of UK Biobank (502,000 participants). This work will also assess for genetic correlation with physical and mental health phenotypes. We will report pathway analyses, expression QTL analyses and Phenotypic Linkage Network analyses. Further, we will assess within the Consortium for Lithium Genomics (ConLiGen) sample whether there is an association between greater polygenic risk of mood instability and lithium response.
Conclusions: This work confirms that mood instability is a polygenic trait which crosses traditional diagnostic categories and opens up the field for further work on the biology of mood instability.
Supported By: Lister Institute Prize Fellowship; Royal College of Physicians of Edinburgh; NARSAD.
Keywords: Depression, Bipolar Disorder, Mood Instability, GWAS

7. Digital Data Capture in the Characterisation of Diurnal Correlates of Mood Instability

Kate Saunders[1], Oliver Carr[1], Amy Bilderbeck[1], Athanasios Tsanas[2], Niclas Palmius[1], Goodwin Guy[1], and Maarten de Vos[1]

[1]University of Oxford, [2]University of Edinburgh

Background: Mood instability and dysregulation of diurnal function are common transdiagnostic features of mental disorder however, the association between them is largely unknown. The emergence of mobile technologies enables us to collect high frequency low friction prospective data. This method of data capture presents the possibility of minimising the inherent bias of retrospective descriptions of psychopathology and allow novel estimates of the underlying diurnal physiology.
Methods: Participants used a bespoke mood monitoring app and wore an actigraphy watch and heart rate (HR) monitor. We collected data from individuals with bipolar disorder (BD, N=20), borderline personality disorder (BPD, N=14) and healthy volunteers (HV, N=20). Phase and amplitude of diurnal rhythms were quantified using a new technique that fitted sinusoids to heart rate (HR) and acceleration signals.
Results: Mood instability was elevated in the patient groups and this was significantly correlated with objectively measured diurnal physiology. Desynchronisation in the phase of diurnal rhythms of HR, sleep and activity were found in BPD. BPD was also associated with increased HR ($p=0.036$) compared to BD and HV. The coherence between mood and the HR, sleep and activity signals showed a high frequency, four cycles per day, component in BD and BPD which was not present in HV.
Conclusions: The digital data streams reveal group-specific physiological phenotypes associated with mood instability and highlight the contribution of diurnal function to mood stabilisation. These findings illustrate the potential of digital data to generate new treatment targets and enable early intervention.
Supported By: Wellcome Trust, Oxford Health NIHR Biomedical Research Centre, RCUK Digital Economy Programme Grant
Keywords: Mood Instability, Diurnal Function, Digital Phenotyping

8. Cognitive and Neural Correlates of Mood Instability

Anna Nobre[1]

[1]University of Oxford

Background: The aim of our study was to understand the relationships between mood instability, cognition, and neural activity.
Methods: Seventy-four participants completed a study lasting ten weeks in which daily measures of mood and performance on a bespoke set of cognitive tasks were obtained using a mobile tablet device. Participants were separated into groups with high (>7) vs. low (<5) scores on the Mood Disorder Questionnaire. Daily measures of mood were obtained using the I-PANAS-SF and cognitive measures focused on the ability to integrate information over time to derive regularities about stimulus-, reward-, and feedback-related contingencies. Neural measures were obtained on separate occasions during the study, and included resting-state scans using fMRI and MEG to reveal the integrity of functional neural networks as well as their degree of dynamical stability over the millisecond time scale.
Results: The results confirmed that the high MDQ group had higher variability on positive and negative mood scores ($F(1,72)>10$, $p<.001$). Both groups showed equivalent ability to extract contextual regularities about non-reward-related contingencies over days, and data about reward-related contingencies are being analysed. Analysis of MEG data revealed changes in oscillatory brain activity according to MDQ groups. Further analyses are exploring changes to the duration of network states in brain.
Conclusions: The results of this study will have important consequences to understanding whether and how instability in mood is linked to instability of neural networks at a fine time scale, and to cognitive instabilities which preclude integration of stimulus-, reward-, and feedback-related contingencies to guide adaptive behaviour.
Supported By: Wellcome Trust
Keywords: Mood Instability, MEG, fMRI Resting State

SYMPOSIUM
New Advances in Translational and Reverse-Translational Addiction Research
12:30 p.m. - 2:30 p.m.
Chair: Rajita Sinha

9. Cue-Induced Incubation of Craving in Human Cocaine Addiction: Modulation by Reappraisal?

Rita Goldstein[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Addiction is a chronically relapsing disorder. Relapse can be precipitated by cues previously associated with drug use. An underlying mechanism encompasses enhanced attention to drug-cues. Event-Related Potentials (ERPs) objectively quantified motivated attention to drug cues as a function of abstinence and self-regulation in individuals with cocaine use disorder (iCUD).
Methods: In the first study, 76 iCUD with varying durations of abstinence (2 days, 1 week, 1 month, 6 months, and 1 year) passively viewed cocaine-related pictures (drug cues) while ERPs were acquired. In the second study, 37 iCUD and 23 healthy controls either viewed cocaine-related pictures normally or down-regulated their reactivity using cognitive reappraisal. ERPs were acquired during the task and eye-tracking (during non-instructed picture gazing) was quantified immediately after each trial to assess change in motivated attention to drug cues after self-regulation.
Results: Amplitude of the late positive potential (LPP) component of the ERP, a measure of motivated attention and a marker of drug-cue reactivity, showed an inverted U-shaped trajectory, such that it increased from 2 days to 1- and 6-months before declining at 1 year (quadratic contrast=-1.13, p=.002). LPPs were reduced during reappraisal compared to normal viewing of drug cues in iCUD ($F=6.56$, $p=0.013$); reappraisal reduced spontaneous gaze duration during viewing of drug-cues in iCUD ($t=2.47$, $p=0.02$).
Conclusions: Unlike self-reported craving, the LPP showed a pattern consistent with incubation of cue-induced reactivity during abstinence. Using cognitive reappraisal strategies reduced such reactivity and generalized to predict reductions in spontaneous attention to drug-cues in iCUD. Impact on relapse prevention remains to be demonstrated.
Supported By: NIDA R01
Keywords: Cocaine Addiction, Craving, Event Related Potentials, Relapse, LPP

10. Epigenetic Enzymes as Novel Therapeutic Targets in Alcohol Addiction

Markus Heilig[1], Claes Wahlestedt[2], Estelle Barbier[1], and Andrea Johnstone[2]

[1]Linköping University, [2]University of Miami Miller School of Medicine

Background: Gene expression in the mPFC is dysregulated in alcohol dependence. We have discovered epigenetic enzymes that take part in dependence-induced reprogramming of the mPFC transcriptome, and may offer a novel class of therapeutic targets.
Methods: Alcohol dependence was induced using chronic intermittent alcohol vapor exposure. RNA-sequencing was used to screen the mPFC transcriptome for persistent differential expression of epigenetic enzymes. PRDM2 was differentially expressed. Molecular consequences of its repression were assessed by measuring H3K9 mono-methylation. PRMD2 expression was knocked down in the mPFC of non-dependent rats using a lenti-viral shRNA vector. Chip-Seq was used to identify PRDM2 regulated target genes as downstream mediators. Functional consequences on addiction-like traits were evaluated by assessing operant self-administration, stress-induced reinstatement of alcohol seeking, and aversion-resistant alcohol seeking.
Results: In dependent rats, the RNA-seq screen identified, qPCR confirmed decreased expression of PRDM2 that was confined to neurons. Alcohol-induced PRDM2 repression was reversed by the DNA methyltransferase inhibitor RG108. Conversely, PRDM2 knockdown in non-dependent rats induced gene expression changes that overlapped with those found following alcohol dependence. These were associated with behavioral consequences otherwise seen following a history of dependence, including escalated alcohol intake, increased resistance to quinine adulteration, and enhanced stress-induced reinstatement. Several genes that exhibited a significant decrease in H3K9me1 enrichment following dependence were identified in the ChIP-seq study, including synaptotagmin 1 (Syt1). We confirmed H3K9me1 enrichment in controls compared to post-dependent rats using ChIP-PCR. All $n>7$, all $p<0.05$
Conclusions: PRDM2 controls behaviors that are critical in alcoholism, and offers a novel therapeutic target.
Supported By: Swedish Research Council
Keywords: Alcohol Addiction, Epigenetics, Stress

11. Orexin-1 Receptor Antagonists as Novel Smoking Cessation Agents

Paul Kenny[1], Theodore Kamenecka[1], George Voren[1], Alexander Duncan[1], Matthew Howe[1], Jonathan Hollander[2], Diane Damez-Warno[1], Qun Lu[2], Purva Bali[1], Roland Burli[3], Ian Gurrell[3], Robert J. Mather[3], and Nicholas J. Brandon[3]

[1]Icahn School of Medicine at Mount Sinai, [2]The Scripps Research Institute, [3]Neuroscience Innovative Medicines, AstraZeneca

Background: Orexin-1 receptors (OX1Rs) regulate the motivation to seek and consume nicotine in laboratory rodents, but underlying mechanisms are unclear. Here, we identify a novel brain circuit through which OX1Rs exerts control over nicotine-seeking behaviors. We also describe progress toward developing patient-ready OX1R antagonists as novel smoking cessation agents.
Methods: Intravenous nicotine self-administration and Intracranial self-stimulation thresholds were used to assess the motivational and reward-related properties of nicotine, respectively. DREADDs were used to chemogenetically activate or inhibit targeted neurons. Fiber photometry was used to monitor orexin neuron activity. CHO cells stably expressing OX1Rs were generated and intracellular calcium responses were used to identify novel OX1R antagonists.
Results: Pharmacological or genetic disruption of OX1 receptor-mediated transmission decreased the motivation to consume nicotine, and attenuated reinstatement of extinguished nicotine-seeking responses, in mice, rats and squirrel monkeys. A population of previously unidentified OX1R-regulated neurons in dorsal thalamus was shown to control nicotine-seeking behaviors. These thalamic neurons do not regulate reward-related actions of nicotine, but instead regulate the apparent “value” of the drug. Based on these findings,

we initiated a drug discovery campaign to develop OX1R antagonists and advance them to human clinical assessment as smoking cessation agents. Progress on this initiative will be summarized.
Conclusions: OX1 receptors regulate the motivational properties of nicotine through a novel thalamic circuit. Targeting this circuit using patient-ready OX1R antagonists represents a novel treatment strategy to facilitate smoking cessation in human tobacco users.
Supported By: NINDS, NIDA
Keywords: Addiction, Drug Discovery, Nicotine Dependence, Reward Circuitry, Chemogenetics

12. Relapse to Methamphetamine Seeking After Choice-Based Voluntary Abstinence (Contingency Management): Role of Central Amygdala and Anterior Insular Cortex

Marco Venniro[1], Daniele Caprioli[1], Michelle Zhang[1], Leslie Whitaker[1], Shiling Zhang[1], Brandon Harvey[1], Carlo Cifani[2], Nathan Mrachant[3], Ofer Yizhar[4], Jennifer Bossert[1], Cristiano Chiamulera[5], Marisela Morales[1], and **Yavin Shaham**[1]

[1]NIDA/IRP, [2]Camerino University, [3]Free University, [4]Weizmann Institute, [5]Verona University

Background: We recently developed a rat model of relapse after choice-based voluntary abstinence that mimics human relapse after cessation of contingency management, a behavioral treatment that uses alternative non-drug rewards to maintain abstinence. Here, we studied the role of central amygdala (CeA) and its afferent projections in relapse after voluntary abstinence.
Methods: We trained rats to self-administer palatable food (6 d) and intravenous methamphetamine (14 d). We then assessed relapse to methamphetamine seeking after 14 voluntary abstinence days (achieved via a discrete choice procedure between methamphetamine and palatable food).
Results: Relapse to methamphetamine seeking after voluntary abstinence was associated with increased expression of the activity marker Fos in CeA but not basolateral amygdala (BLA). Systemic injections of the dopamine Drd1-family receptor antagonist SCH39166 decreased relapse and CeA Fos expression; in situ hybridization showed higher co-labeling of Fos with Drd1 than with Drd2. CeA SCH39166 injections decreased relapse after voluntary abstinence; in contrast, BLA SCH39166 injections or CeA injections of the dopamine Drd2-family receptor antagonist raclopride were ineffective. Double-labeling of Fos with the retrograde tracer cholera toxin subunit-B (CTb, injected in CeA) demonstrated that relapse after voluntary abstinence was associated with selective activation of ventral anterior insula (AIV)→CeA projection. AIV inactivation with GABA receptor agonists or chemogenetic inactivation of AIV→CeA projection decreased relapse after voluntary abstinence. Electron microscopy data showed that AIV vGluT1-expressing projection-neurons form excitatory asymmetric synapses on CeA neurons.
Conclusions: Our data demonstrate a critical role of CeA Drd1 and the AIV→CeA glutamatergic projection in relapse after cessation of contingency management-induced voluntary abstinence.
Supported By: NIDA-NIH
Keywords: Relapse, Drug Addiction, Contingency Management, Central Amygdala, Anterior Insular Cortex

SYMPOSIUM
Genomic, Proteomic, Cellular Underpinnings for Postsynaptic Density Pathophysiology in Schizophrenia

12:30 p.m. - 2:30 p.m.
Chair: Chang-Gyu Hahn
Co-Chair: Sabina Berretta

13. Dysregulation of Coding and Non-Coding Transcripts Points to Synaptic Abnormalities in Schizophrenia

Panos Roussos[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Transcription of enhancer RNAs (eRNAs) takes place at a broad range of regulatory sequences in an activity dependent manner. A subset of putative enhancers enriched in disease-associated variants is often transcriptionally active in pathologically relevant cell types. It is unclear whether the alteration of eRNA transcription: (i) has an active role in disease-associated enhancer malfunction and (ii) drives downstream dysregulation in coding transcripts.
Methods: We used transcriptomic and epigenomic data to interrogate how genetic variants can alter enhancer transcriptional activity in the human brain. We combined RNA-seq data from 537 post mortem brain samples from the CommonMind Consortium with cap analysis of gene expression and enhancer identification, using the assay for transposase-accessible chromatin followed by sequencing (ATAC-seq).
Results: We find 118 differentially transcribed eRNAs in schizophrenia and identify schizophrenia-associated gene/eRNA co-expression modules which are enriched in post-synaptic density markers. In addition, we identify 58,140 genetic variants affecting expression of 927 enhancers, which we refer to as enhancer expression quantitative loci, or eeQTLs. We find enhancer expression to be consistent across studies and validate differentially expressed eRNAs and eeQTLs. Further, combining the eeQTLs with a genome-wide association study of schizophrenia leads to identification of a genetic variant that, through altered enhancer function, affects expression of a target gene, GOLPH3L.
Conclusions: We found replicable differences in the transcribed eRNAs in schizophrenia that converge to common biological processes.
Keywords: Gene Expression, Enhancer, Quantitative Trait Loci (QTL)

14. Glutamatergic Signaling and PSD Proteome in Schizophrenia

Chang-Gyu Hahn[1]

[1]University of Pennsylvania

Background: The postsynaptic density (PSD) harbors multiple pathways implicated for schizophrenia and is the epicenter of dendritic spines. Critical to PSD pathophysiology are alterations in signaling and PSD proteome and their relationship. We analyzed Src kinase hypoactivity as a molecular signature of GluN hypofunction and its association with PSD proteome dysregulation in schizophrenia.
Methods: Synaptic membranes (SPM) and PSD fractions were derived from the dorsolateral prefrontal cortex (DLPFC), nucleus accumbens (NA) and amygdala from the cohort of 21 matched pairs of schizophrenia and control subjects. PSD fractions were examined for Src kinase activity, GluN1 co-immunoprecipitation and quantitative proteomics employing LC-SRM/MS with the [13C6] brain ISTD.
Results: Src activity was decreased in all three regions of the patient group ($p<0.03$ in all regions), while the stoichiometry of GluN complexes differed between regions. The patient group showed that groups, glutamate receptors, endocytosis and presynaptic vesicles were altered all three regions; yet different molecules in each region. The ratios of proteins in the PSD over those in the whole tissue homogenates, were strikingly altered in adhesion molecules, and scaffolding proteins ($P<0.01$ for each), suggesting a role of intracellular trafficking.
Conclusions: GluN hypofunction affects brain regions broadly, while their molecular underpinnings may vary between regions. Such signaling alterations can be traced to PSD proteome, in which each molecular alteration may be subtle yet highly significant when clustered for functional groups. Study of protein- protein interactions amongst these molecules will connect dots between signaling and proteome changes in the PSD in schizophrenia.
Supported By: MH-075916
Keywords: Postsynaptic Density, Src Kinase, Targeted Proteomics, Postmortem Human Brain Tissue, NMDAR Hypofunction

15. The Tetrapartite Synapse in Schizophrenia: Role of the Extracellular Matrix and Glial Cell in PSD Pathology

Sabina Berretta[1], Harry Pantazopoulos[1], and Gabriele Chelini[1]

[1]McLean Hospital, Harvard Medical School

Background: The 'tetrapartite synapse', comprised of the pre- and post-synaptic elements, glia and the extracellular matrix (ECM), may represent a useful concept to investigate synaptic abnormalities in schizophrenia (SZ). Interactions between the ECM, which forms organized perisynaptic aggregates, and glial cell have been shown to regulate synaptic functions and plasticity. These mechanisms are mediated by ECM remodeling proteases, such as matrix metallo proteases (MMPs) and cathepsin S. We tested the hypothesis that previously shown decreases of perineuronal nets (PNNs), a form of perisynaptic ECM, and CS-6/Glia clusters, an ECM structure enriched in 6-sulfated chondroitin sulfate proteoglycans, in SZ may be at least in part due to a disregulation of ECM remodeling proteases. Studies in human and rodents assessed the relationship between CS-6 expression, glia and synapses.
Methods: Amygdalas from control ($n=16$) and SZ ($n=20$) subjects were used to test expression of MMP9, MMP16 protein (western blotting) and cathepsin S mRNA (QRT-PCR). Mouse and healthy human amygdala were used to investigate CS-6/Glia clusters.
Results: Protein expression of MMP9 and MMP16 was increased in the amygdala of people with SZ ($p=0.02$ and $p=0.04$, respectively). Cathepsin S mRNA was decreased in SZ ($p=0.03$). CS-6/Glia clusters consist of astrocyte processes carrying CSPG/CS-6 and surrounding dendritic spines.
Conclusions: CS-6/Glia clusters, decreased in SZ, may represent microenvironments involved in synaptic regulation. Group comparison show disregulation of ECM remodeling enzyme expression in the amygdala of subjects with SZ. We suggest that these abnormalities may contribute to decreases of PNN and CS-6/Glia clusters in SZ and to PSD pathology in this disorder.
Supported By: NIH R01 MH104488; NIH R01 MH086522
Keywords: Schizophrenia, Synapse, Extracellular Matrix, Matrix Metalloproteases, Microglia

16. Synaptic Mechanisms in 16p11.2 Duplication Model Mice

Peter Penzes[1], Jeffrey Savas[1], and Marc Forrest[1]

[1]Northwestern University

Background: Duplications of 16p11.2 chromosomal region, found in autism spectrum disorders (ASD), schizophrenia (SZ), intellectual disability (ID), Rolandic epilepsy, and other disorders, are among the top CNVs in SZ. Alterations in glutamatergic synapses are key pathogenic mechanisms in SZ, ASD, and ID; yet how synaptic biology contributes to the pathogenesis of CNV disorders remains largely elusive.
Methods: We have used cultured neurons and mouse models, proteomics and structured illumination microscopy (SIM).
Results: While alterations in gene networks in CNVs have been extensively investigated through mRNA expression profiling, alterations in protein networks, have not been investigated. To gain insight into global alterations in synaptic proteins in 16p11.2 duplication vs. controls, we performed a quantitative mass spectroscopy proteomic analysis of synaptosomal preparations from dp/+ vs. wt mice. Pathway and network analysis identified ion channels and SNARE proteins as top GO categories. Remarkably, subunits of AMPA type glutamate receptors were among the upregulated proteins. To model the psychiatric risk profile of synaptic alterations, we compared the dysregulated proteins with sets of published exonic de novo mutations for each. Surprisingly, we found a substantial enrichment of risk factors for epilepsy and ASD but not ID and SZ.

Conclusions: We show for the first time that subcellular compartment-specific proteomics can be harnessed to identify novel mechanisms whereby a driver within the CNV can regulate a protein network outside of the CNV, PSD pathways in particular. Such cellular compartment-specific protein network alterations could underlie specific disease subphenotypes.
Supported By: NIH R01
Keywords: Synapse, Excitability, Schizophrenia, Autism

SYMPOSIUM
New Perspectives on the Study of Early Life Stress
12:30 p.m. - 2:30 p.m.
Chair: Joan Kaufman

17. Lifelong Transcriptional, Epigenetic, and Neurophysiological Consequences of Early Life Stress in Mouse Brain Reward Circuitry

Catherine Pena[1], Hope Kronman[1], Allyson Friedman[2], Deena Walker[1], Hannah Cates[1], Orna Issler[1], Yong-Hwee E. Loh[1], Rosemary Bagot[3], Aarthi Ramakrishnan[1], Immanuel Purushothaman[1], Yingbo Zhu[1], Rachael Neve[4], Li Shen[1], Eric Nestler[1], and Ming-Hu Han[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Hunter College, [3]McGill University, [4]Massachusetts General Hospital

Background: Abuse, neglect, and other forms of early life stress (ELS) increase risk for depression. We recently established a "two-hit" stress paradigm in male and female mice, and found a sensitive period for postnatal stress to increase risk that stress in adulthood results in depression-like behavior. We sought to understand the long-lasting consequences of ELS on reward circuitry at transcriptional, epigenetic, and neurophysiological levels.
Methods: Mice were standard-reared or exposed to ELS from P10-17. RNA-seq (n=4-6 samples/group) was performed in adult male and female ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex, and analyzed by standard and custom pipelines. ChIP-seq (n=4) was performed in adult male VTA. VTA Otx2 was virally manipulated by HSV infection in vivo (n=6-10/group). VTA dopamine neuron firing was measured by cell-attached recordings in slice preparation.
Results: Even prior to behavior changes, early life stress increases VTA dopamine neuron firing rate in adult mice (n= 6-8 mice, $p<0.05$), and alters genome-wide transcriptional patterns, to be similar to those from mice exhibiting depression-like behavior after adult stress. We found a causal and temporal relationship between the transcription factor OTX2 and stress susceptibility, and a postnatal sensitive window for down-regulation of Otx2 to cause enduring stress sensitivity ($p<0.05$). VTA Otx2 may mediate the changes in dopamine neuron physiology (n=5-7, $p<0.05$). ChIP-sequencing for H3K4me3 indicates genome-wide epigenetic priming of transcriptional responses to additional stress.
Conclusions: This multi-level integrative approach provides novel insights into the mechanisms by which early life stress primes long-lasting changes in reward circuitry and enhances vulnerability to depression.
Supported By: K99MH115096; P50 MH096890; R21MH112081; Hope for Depression Research Foundation
Keywords: Early Life Stress, Ventral Tegmental Area, RNA Sequencing, Epigenetics, Depression

18. Dysregulation of Non-Cg Methylation by Child Abuse

Pierre-Eric Lutz[1], Marc-Aurele Chay[1], Jean-Francois Théroux[1], Tony Kwan[1], Adriana Redensek[1], Naguib Mechawar[1], Tomi Pastinen[1], and **Gustavo Turecki**[1]

[1]McGill University

Background: Child abuse associates with increased lifetime risk of negative mental health outcomes. A growing number of studies suggest a relationship between child abuse and lifetime morphological and functional changes in the amygdala, and these changes are likely mediated by epigenetic regulation.
Methods: Using postmortem brain tissue from a well-characterized cohort of subjects with histories of severe child abuse (N=21) and normal controls (N= 17), we conducted whole genome bisulfite sequencing (WGBS-Seq), RNA-Seq and Chip-Seq (H3K4me1, H3K4me3, H3K27ac, H3K36me3, H3K9me9 and H3K27me3) to obtain a comprehensive map of epigenetic changes in the amygdala associated with child abuse. Results were then validated and replicated in an extended and independent cohort (N=88)
Results: Results indicated that, surprisingly, a history of child abuse associates with epigenetic adaptations that are as frequent in the CAC as in the reference CG context. By incorporating information on histone modification in the DNA methylation analysis, we observed that the cross-talk between these 2 epigenetic layers strikingly differs among CG and CAC contexts. Importantly, we also found that differentially methylated regions associated with child abuse occur in distinct chromatin states in the CG and CAC contexts. We then further investigated the most significant differentially methylated regions that showed evidence of functional impact at transcriptional level. These results were technical validated, and subsequently, replicated in an independent cohort of individuals.
Conclusions: Our results unravel a previously uncharacterized source of epigenetic plasticity in the brain, which may help us explain the lifelong impact of early-life adversity on brain function.
Supported By: CIHR
Keywords: Early Life Adversity, Epigenetics, Human Postmortem Brain, DNA Methylation, Non-CpG Methylation

19. Hazards to Early Development: The Biological Embedding of Early Life Adversity

Charles Nelson[1]

[1]Boston Children's Hospital/Harvard Medical School

Background: The number of children under 18 years has increased worldwide over the past decade. This growth spurt is due, in part, to remarkable progress in child survival. Alas, surviving early hazards like prematurity or infectious disease does not guarantee that children's development will not be compromised by other hazards as they grow older. Throughout the world, children continue to be confronted with a large number of biological and psychosocial challenges that greatly limit their developmental potential.
Methods: In this talk I will focus on two strands of work that reflect very different types of adversity: the effects of early, profound psychosocial deprivation and the effects of growing up in a low resource urban center where children are exposed to a large number of both biological (e.g., malnutrition) and psychosocial (maltreatment) stressors. In the case of the former, I will review the most recent findings from the Bucharest Early Intervention Project, a randomized controlled trial of foster care as an intervention for early institutionalization. In the case of latter, I will review recent findings from a large study taking place in Dhaka, Bangladesh, where a variety of biological (e.g., inflammation) and neuroimaging measures (e.g., EEG, fNIRS, MRI) are being obtained.
Results: Collectively, the research demonstrates the differential effects of neglect vs. adversity on different biological and behavioral systems.
Conclusions: The data highlight the value of conceptualizing neglect as an absence of species expectant-experience that compromises neuronal processes during sensitive periods, and studying the effects of other adversity utilizing stress-research frameworks
Supported By: NIMH; Bill and Melinda Gates Foundation
Keywords: Brain Development and Aging, Abuse and Neglect, Childhood Adversity, Early Life Stress

20. Child Abuse and Epigenetic Mechanisms of Disease Risk

Janitza Montalvo-Ortiz[1], Joel Gelernter[2], Nicholas Wymbs[3], Robert Althoff[4], James Hudziak[4], Hongyu Zhao[5], and Joan Kaufman[6]

[1]Yale School of Medicine/VA CT Healthcare Center, [2]Yale University, [3]Kennedy Krieger Institute, [4]University of Vermont, [5]West Haven VA Medical Center, [6]Kennedy Krieger Institute/Johns Hopkins Medical Institute

Background: Child abuse and other adverse childhood experiences are associated with increased risk for a broad range of psychiatric and medical health problems. There is growing evidence that child abuse confers risk for these deleterious outcomes through epigenetic mechanisms.
Methods: Saliva DNA specimens were processed using the Illumina 450K BeadChip in our Connecticut (N=192) and Vermont (N=233) cohorts of maltreated and comparison children. A subset of the children recruited from Vermont also completed a multimodal imaging protocol.
Results: After controlling for race, sex, age, cell heterogeneity, and population stratification using three principal components: 1) OTX2 methylation, together with measures of childhood adversity, significantly predicted depression in the children; extending the findings Dr. Péna and colleagues reported in their mouse study of early life stress; 2) LINGO3 methylation, together with measures of childhood adversity likewise predicted depression in the children, as well as functional connectivity from the anterior cingulate cortex (ACC), extending Dr. Turecki and colleagues findings generated from postmortem ACC tissue in suicide victims with histories of child maltreatment; 3) at the level of whole genome significance (5.0 x 10-7), methylation in HPCAL4, a gene involved in neuronal development and calcium signaling, predicted aggressive behavior in the children; and 4) also at the level of whole genome significance, methylation values in multiple known obesity-risk genes interacted with the adversity measure to predict BMI in the children. Replication of research findings occurred across and/or within separate subsamples of the Connecticut and Vermont cohorts.
Conclusions: Ongoing translational research will help to further elucidate these mechanisms.
Supported By: RO1 MH077087, RO1 MH098073, NARSAD Young Investigator Award to JLMO
Keywords: Epigenetics, Child Abuse, Depression, Aggression, Obesity

SYMPOSIUM
Using Electrophysiology in Single-Gene Disorders to Inform Biomarker Discovery for Idiopathic ASD

12:30 p.m. - 2:30 p.m.
Chair: Alexander Kolevzon
Co-Chair: Jennifer Foss-Feig

21. Auditory EEG Phenotypes in Single Gene Disorders: Insight into Heterogeneity in Idiopathic Autism

Lauren Ethridge[1], Elizabeth Berry-Kravis[2], Andrew Thaliath[2], Emily Isenstein[3], Allison Durkin[3], Charles Nelson[4], Lauren Baczewsi[4], Craig Powell[5], Stormi White[5], Matthew Mosconi[6], Ernest Pedapati[7], Craig Erickson[7], and John Sweeney[8]

[1]University of Oklahoma Health Sciences Center, [2]Rush University Medical Center, [3]Icahn School of Medicine at Mount Sinai, [4]Boston Children's Hospital/Harvard Medical School, [5]UT Southwestern Medical Center, [6]University of Kansas, [7]Cincinnati Children's Hospital, [8]University of Cincinnati

Background: Sensory processing abnormalities are common, clinically distressing features of iASD and associated single-gene disorders, but little is known about their underlying biology. Sensory hypersensitivity is common in Fragile X Syndrome (FXS) however Phelan McDermid Syndrome (PMS) is more strongly characterized by reduced sensory reactivity.
Methods: Adolescents and adults with FXS (n=21) and matched neurotypical controls (n=21) completed a resting period, chirp modulated auditory task, and modified auditory gating task during dense-array EEG. Pilot auditory gating EEG data in PMS (n=18) was also collected. Time-frequency, phase-amplitude coupling and event-related potential (ERP) amplitude were assessed.

Results: FXS showed decreased habituation of the N1 event-related potential response F(1,27)=6.9, P=0.014 and increased gamma power F(1,27)=10.1, p=0.004 coupled with decreases in gamma phase-locking during the early-stimulus registration period t(27)=3.19, P=0.004 and during the chirp stimulus t(32)=2.8, p=.008. EEG abnormalities in FXS were associated with heightened sensory sensitivities and social/communication deficits, suggesting possible insight into similar reports in iASD. PMS showed decreased habituation and prolonged ERP latency t(23)=3.47, p=.002. While FXS early-stimulus processing was characterized by increased amplitude ERPs, PMS ERPs were reduced in amplitude.
Conclusions: Dissociable ERP amplitude abnormalities may be associated with the specific biological pathways affected in FXS and PMS. Habituation deficits are more universal. The combination of deficits presenting at the individual level may provide insight into iASD heterogeneity. Sensory processing-related EEG abnormalities are simple to administer, clinically relevant and parallel preclinical findings in KO mouse models, supporting their potential use as translational biomarkers for elucidating individual iASD biology as well as novel treatment evaluation.
Supported By: NIMH/NICHD grant U54 HD082008-01; Phelan McDermid Syndrome Foundation Pilot Grant
Keywords: Autism Spectrum Disorder, EEG, Fragile X Syndrome

22. Non-Word Memory in Rett Syndrome and Rett-Related Disorders

Sarika Peters[1], Dorita Jones[1], and Alexandra Key[1]

[1]Vanderbilt University Medical Center

Background: Despite significant advances at the level of basic research that have progressed to treatment trials, sensitive biomarkers of higher-level cognitive and language processing deficits in Rett and RTT-related disorders remain elusive. To test whether EEG could be used to dissociate capacity for auditory learning and memory, we assessed how children with RTT and MECP2 duplication syndrome became familiarized with a repeatedly presented spoken non-word, testing whether differentiation of familiarized vs. novel non-word stimuli could be detected with event-related potentials (ERP).
Methods: Participants were presented with a total of 100 Nonword trials (50 = word was said once, and 50= repeated word). We hypothesized that repeated non-words would elicit more positive parietal responses than novel words.
Results: 32 TD participants, 7 with MECP2 Duplication syndrome, and 13 with RTT provided usable data. The TD group and the MECP2 duplication group show the expected sign of incidental memory for repeated > once presented nonwords at the parietal scalp at 250-500ms (t=-2.55; p=.04 in MECP2 dup, t=-3.970; p<.001 in TD). Better discrimination was related to better receptive language in TD (r=.48; p<.05) and MECP2 dups, but increased behavioral severity (r=.96; p=.03) in MECP2 dups. RTT participants did not resemble either group, and results were not significant at any time window.
Conclusions: This passive auditory memory task differentiated between Rett-related neurogenetic disorders, and performance was related to receptive language and behavioral severity. This task could have applicability to other nonverbal, lower-functioning populations as well as iASD. Different neural signatures may relate to levels of MeCP2 expression.
Supported By: Rettsyndrome.org
Keywords: Event Related Potentials, Rett Syndrome, Auditory Processing, MECP2

23. Biomarker Discovery in ASD: Visual Evoked Potentials as a Biomarker of Phelan-McDermid Syndrome

Paige Siper[1], Julia George-Jones[2], Stacey Lurie[3], Mikaela Rowe[1], Allison Durkin[1], Jordana Weissman[1], Kristin Meyering[1], Audrey Rouhandeh[1], Joseph Buxbaum[1], and Alexander Kolevzon[1]

[1]Seaver Autism Center at the Icahn School of Medicine at Mount Sinai, [2]University of Texas at Austin, [3]Yeshiva University

Background: Excitatory/inhibitory imbalance represents one promising mechanistic hypothesis for autism spectrum disorder (ASD). Impairments in excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission can be measured through electrophysiology (EEG) and targeted through pharmacological intervention. Visual evoked potentials (VEPs) reflect the sum of excitatory and inhibitory postsynaptic activity. Applying a genetics-first approach allows us to examine single-locus causes of ASD, such as Phelan-McDermid syndrome (PMS), where genetic alterations are known to directly impact glutamatergic circuitry.
Methods: A contrast-reversing checkerboard was used to elicit transient VEPs (tVEPs) in 2-18 year old children (25 PMS, 50 idiopathic ASD (iASD), 44 typically developing (TD) controls). tVEP response changes were also assessed during a 12-week clinical trial of insulin-like growth factor 1 (IGF-1) in PMS (n=6).
Results: Amplitude at P60-N75 (p<.001) and N75-P100 (p=.001), reflecting excitatory and inhibitory activity respectively, were significantly smaller in iASD versus TD. The PMS group displayed distinct tVEP waveforms, including significantly attenuated P60-N75 responses (p<.001, $\eta p2$=.782) and decreased low gamma activity, indicating a specific, dissociable VEP signature. A significant increase in low gamma activity relative to baseline (p=.048) was observed following IGF-1 treatment in a sample of six individuals with PMS.
Conclusions: Our results are consistent with findings from animal models, which demonstrate the deleterious effects of SHANK3 deficiency on glutamatergic function. The increase in high frequency responses observed during our clinical trial reflects enhanced excitatory brain activity. VEPs represent a promising biomarker of both target engagement and treatment response.
Supported By: NIH, Phelan-McDermid Syndrome Foundation, Seaver Foundation
Keywords: Autism Spectrum Disorder, EEG, Biomarkers, Phelan-McDermid Syndrome, Visual Evoked Potential

24. Biomarker Development in ASD: Electrophysiological Response During Auditory Gap Detection is Associated With Symptom Severity and May Index Excitatory/Inhibitory Imbalance

Jennifer Foss-Feig[1], Sylvia Guillory[1], Wendy Stone[2], Mark Wallace[3], and Alexandra Key[3]

[1]Icahn School of Medicine at Mount Sinai, [2]University of Washington, [3]Vanderbilt University

Background: Several rare genetic disorders that result in an ASD phenotype (e.g., Fragile X syndrome, Phelan-McDermid syndrome) implicate alterations in excitatory/inhibitory neurotransmitter balance. Recently, the search for sensitive and reliable biomarkers indexing specific neural processes and relevant for measuring treatment response has intensified in ASD research. Auditory gap detection is a low-level sensory function that: a) is impaired in ASD and other communication disorders, b) is sensitive to perturbations in E/I balance, and c) can be indexed with electrophysiology (EEG). This study tested whether electrophysiological response during gap detection is impaired in ASD, associated with clinical variables, and a potentially viable biomarker for ASD.
Methods: EEG data was recorded from 10-13 year old children (15 ASD; 17 typically developing [TD]) during a gap detection task. Amplitude and latency of N1 and P2 event-related potentials were evaluated for near-threshold (3ms) gaps in 1000ms white-noise stimuli as a function of whether gaps were behaviorally-detected. In parallel, measures of sensory, receptive language, and diagnostic functioning were administered.
Results: Central P2 amplitude was larger for ASD than TD regardless of detection accuracy ($F1,30=8.57$, $p=0.006$). Attenuated P2 related to more auditory processing abnormalities ($r21=0.45$, $p=0.043$), poorer sensory registration ($r21=0.63$, $p=0.002$), and weaker receptive language ($r19=0.44$, $p=0.057$) across groups, and to more ASD language/communication symptoms in ASD ($r15=-0.54$, $p=0.026$).
Conclusions: Electrophysiological response during auditory gap detection is altered in ASD and associated with clinical symptoms. It may offer a useful biomarker in subpopulations with disrupted E/I balance, and for measuring response to pharmacological manipulations of excitatory and/or inhibitory neurotransmitters.
Supported By: Autism Speaks Dennis Weatherstone Predoctoral Fellowship, NARSAD Young Investigator Award, Seaver Autism Foundation
Keywords: Autism Spectrum Disorder, Biomarkers, EEG, Auditory Perception, Neurogenetic Syndromes

SYMPOSIUM
Reproducibility in Psychiatric Neuroimaging: Big Data for Big Problems
12:30 p.m. - 2:30 p.m.
Chair: David Kennedy

25. Combining Data Resources to Elucidate Subtle Details of Brain Development

Jean Frazier[1], Steven Hodge[1], J.B. Poline[2], and David Kennedy[1]

[1]UMass Medical School, [2]Montreal Neurological Institute and Hospital

Background: The neuroimaging literature is replete with statistically significant, but minimally differentiating imaging results; these findings include 'approximate replications' reported in ways that neither confirms nor refutes any of them. The prevalence of underpowered studies and positive-finding publication bias combine to exacerbate this problem.
Methods: Using the shared data of PING, ABIDE and PEDS, and a specific structural analysis workflow (FreeSurfer), we can ask for a given anatomic question (is there a gender effect in the volume in the volume of the hippocampus in typically developing children) what is the dependency and consistency of the result as a function of statistical model selection. We generate an ensemble of statistical models to determine gender effect in this data that include all combinations of: data source, age, site, socioeconomic status (SES), intracranial volume (ICV) or total brain volume (TBV), and genetic ancestry factor (GAF).
Results: Overall, this study includes data from ~1800 participants, aged 4-20. Theobservation of the sex effect in the hippocampus is seen to evolve as the various studies are combined to reach this final cohort. Substantial shifts are seen in model predictive accuracy with the specific inclusion of site, ICV/TBV and GAF. Most of the comprehensive models indicate a significant, but small gender effect (~200mm3) with an R2 in the [.4 - .5] range.
Conclusions: These results demonstrate that, even prior to considering the subtle modulations caused by diagnostic effects of developmental disorders, careful attention to data model and data sources are needed to definitely document developmental factors in brain structures.
Supported By: R01 MH083320, P41 EB019936
Keywords: Brain Development, Computational Modeling, Data Sharing, Reproducibility

26. The Impact of Data Science on the Integration and Reporting of Experiments

Smruti Padhy[1], David Kennedy[2], and Satrajit Ghosh[1]

[1]Massachusetts Institute of Technology, [2]University of Massachusetts Medical School

Background: In experimental research, data integration happens locally. A typical experiment manages multiple streams of information (imaging, clinical, etc.). Annotating, recording, and integrating information across sources and analyses is difficult. BrainVerse is a tool that assists with semantic integration and visualization of information to support local and global data and results management.
Methods: While BrainVerse is designed to support information management generally, we demonstrate its integrative features by looking at the effect of software selection for the study of cortical thickness in autism. We integrated cortical thickness measurements of the Desikan-Killany-Tourville (DKT) atlas from 1112 ABIDE cases using FreeSurfer 5.1/5.3, and ANTS. We generated a consistent representation over numerous features including age, gender, diagnosis, site, tool, version, anatomical region, etc. We then tested if software had an effect on regional measures.

Results: Results include the correlation of each of the anatomic regions in the atlas across each of the analysis methods. The FreeSurfer 5.1-5.3 correlation coefficients averaged 0.87 [0.76-0.93], and the FreeSurfer 5.3-ANTS correlation coefficients averaged 0.47 [0.19-0.67]. Of the 62 DKT regions, 16 showed discordant 'significance' of the diagnosis effect (FreeSurfer $p < 0.05$ and ANTS $p > 0.05$ or vice versa).
Conclusions: Comprehensive data integration that facilitates comparison across experimental details is critical to developing a more complete understanding of the research results, both within and across studies. BrainVerse provides a tool that supports the annotation of experimental results with the necessary metadata needed to increase reproducibility of neuroimaging studies.
Supported By: P41 EB019936
Keywords: Reproducibility, Cortical Thickness, Software Tools, Data Modelling, Semantic Integration

27. Variability of the Neuroimaging Results Across OS, and How to Avoid it

Yaroslav Halchenko[1], Satrajit Ghosh[2], J.B. Poline[3], Dorota Jarecka[2], and David Kennedy[4]

[1]Dartmouth College, [2]Massachusetts Institute of Technology, [3]Montreal Neurological Institute and Hospital, [4]University of Massachusetts Medical

Background: Any data collection and analysis involves software. Given the same data and the same analysis workflow, the same software can produce different results depending on the version of the software or environment. Such variability hinders the reproducibility and undermines the validity of the findings. Given prevalent small study sample sizes and effects of interest, controlling such confounds is important.
Methods: We studied the aspects of software environments which matter most to guarantee correct and reproducible results, and developed software solutions (NeuroDebian, NeuroDocker, NICEMAN, etc.) which could assist neuroimagers to gain better control over their data, software, and results. We used these management functions to run a simple FSL-based volumetric analysis on identical data (24 publicly available subjects) under multiple operating systems and examined the numeric similarity of the results obtained.
Results: All runs using a Docker-ized (Debian 8.7) version of the workflow, regardless of base operating system and on 'natively' running Ubuntu 14.04 (both using NeuroDebian repository), yielded identical, re-executable results. Native operation on the Mac OSX yielded different numerical voxel counts across all structures and subjects. Although the correlations of the volumetric results in aggregate across the population is very high (0.918-1.000), we see a range of volumetric differences (0.0-7.7%) that spans a large percentage of structure volume.
Conclusions: We advocate the aforementioned solutions to improve efficiency and correctness of the neuroimaging research. This provides a more structured framework to examine the generalizability of the findings in the future.
Supported By: NIH P41
Keywords: Brain Imaging, fMRI, Reproducibility, Software Platform

28. The Neuroscience Big Data Landscape and FAIR

Maryann Martone[1] and Jeffrey Grethe[1]

[1]University of California, San Diego

Background: The Neuroscience Information Framework (NIF) launched in 2008 to survey resources and databases for neuroscience (NIF Registry) and provide an information framework for promoting discovery and integration across databases (NIF data federation). Here we use NIF data to provide insight into the neuroscience data landscape, and how it measures up to the FAIR Data Principles, gaining broad adoption across biomedicine. FAIR aims to make data: Findable, Accessible, Interoperable and Reusable for humans and computers.
Methods: We evaluated the NIF Registry and data federation to check the stability of links (F), programmatic access and stability of metadata (A), use of standard vocabularies (I) and availability of clear licenses [R].
Results: Of the 13,000 digital resources cataloged, 3% no longer exist, 10% have moved location at least once. About 50% of data resources have terms of use, but only ~5% list specific licenses. Analysis of use of community ontologies in the federation indicates very low utilization. Comparing metadata terms used by data sources against the NIF ontologies suggests adequate vocabularies for major domains, e.g., neuroanatomy, and not others, e.g., techniques.
Conclusions: This analysis provides insight into current practices for building and maintaining digital resources, and point to immediate steps that can improve FAIR compliance, e.g., use of clear licenses. Others involve more community effort, e.g., use and development of standards. The analysis also highlights the critical role of aggregators like NIF and NITRC for providing stability in the dynamic digital landscape by preserving records and data for discontinued resources.
Supported By: P41 EB019936, U24 DA039832
Keywords: Standards, Reproducibility, Big Data, Data Integration

SYMPOSIUM
Heart-Brain Connections: The Role of the Periaqueductal Gray (PAG) in Passive and Active Fear

12:30 p.m. - 2:30 p.m.
Chair: Karin Roelofs
Co-Chair: Elizabeth Phelps

29. Central Amygdala and Periaqueductal Grey Circuits for Active and Passive Responses to Threat

Philip Tovote[1], Jonathan Fadok[2], Soledad Esposito[3], Paolo Botta[4], Sabine Krabbe[3], Cyril Herry[5], Silvia Arber[3], and Andreas Luthi[3]

[1]University Hospital Wurzburg, [2]Tulane University, [3]Friedrich Miescher Institute, [4]Columbia University, [5]Centre Magendie

Background: Behavioral responses to threat encompass evolutionarily conserved active or passive defensive motor

responses, such as flight and freezing, respectively. The central nucleus of the amygdala (CEA) and midbrain periaqueductal grey (PAG) are important parts of the circuitry that underlies top-down control of the defense reaction to threat. Defensive action selection has been modelled around the concept of threat imminence, but the circuit mechanisms mediating different defensive behaviors and the switch between them remain unclear.
Methods: We combined behavioral assays for learned and innate fear, intersectional optogenetics, in vivo and in vitro electrophysiology, as well as the latest rabies virus-mediated anatomical tracing technology to characterize neuronal circuits underlying passive and active fear coping styles, both in the CEA and PAG of mice.
Results: We identified specific neuronal subtypes and projection pathways mediating freezing or flight, and the switch between them. In the CEA, an inhibitory microcircuit between cells expressing corticotropin-releasing-factor (CRF, n=23, P<0.01, Chi2) and somatostatin (SOM, n=24, P<0.01, Chi2)-positive neurons gate freezing-to-flight transitions. A CEA-to-PAG dis-inhibitory circuit mechanism mediates freezing through excitatory projections from PAG to the magnocellular nucleus of the medulla (Mc, n=7, P<0.05, Wilcoxon).
Conclusions: Our data suggests that CEA and PAG output selection is mediated by integration of local microcircuit interactions and external inputs. Behavioral and autonomic aspects of the defensive response are parsed into different output pathways from the PAG. Our findings demonstrate that defensive action selection is a cue- and context dependent, multi-site process involving complex functional motifs within evolutionary old, mammalian "survival circuits".
Supported By: Swiss National Science Foundation, Brain & Behavior Foundation, German Research Community
Keywords: Fear and Anxiety, Periaqueductal Grey, Central Amygdala, Defensive Behavior, Freezing and Flight

30. Neural Switch Between Passive and Active Fear in Humans: Alterations in and Development of Stress-Related Symptoms

Karin Roelofs[1], Mahur Hashemi[1], Reinoud Kaldewaij[1], Wei Zhang[1], Saskia Koch[1], and Floris Klumpers[1]

[1]Donders Institute, Centre for Cognitive Neuroimaging, Radboud University

Background: Recent animal and human studies have suggested that the parasympathetic state of freezing may facilitate action-preparation and decision-making under acute threat and is essential for adequate stress-coping. However, the neurocognitive mechanisms supporting freezing and the neural switch to sympathetically-driven actions remain unclear in humans. In addition, their role in the development of anxiety symptoms remains unexplored.
Methods: In two independent studies in unselected civilians (N=22) and police recruits (N=54), respectively, we applied fMRI and autonomic measurements while participants performed an active defensive (Go/No-go) task under threat of electric shock. In addition, we tested 340 police officers before and after trauma-exposure on the same task in light of a longitudinal stress-resilience study.
Results: Anticipation on action decisions under threat elicited freezing, evidenced by parasympathetic heart-rate slowing (P<.001), periaqueductal gray activity (PAG) and PAG-amygdala connectivity (Ps<.05-SVC). Crucially, stronger PAG-activity during action preparation predicted faster accurate responses (Rs>.37, Ps<.05). The switch from freezing to action was associated with specific and consistent perigenual anterior cingulate cortex (pgACC) activity and pgACC-amygdala connectivity (Ps<0.01-FWE). Anxiety was related to stronger freezing in police-officers (longitudinal trauma-study (N=340): R=.12, P<.05).
Conclusions: These findings show that freezing-related PAG activity supports decision-making by facilitating action preparation and highlight the role of the pgACC when critical switching from freezing to action under threat is required. These results translate animal models on the neural switch form freeze-to-action to humans and provide potential biomarkers for stress-resilience. They will be discussed in light of ongoing longitudinal studies on the role of deviant freezing-responses in stress-coping and the development of anxiety-symptoms.
Supported By: This work was supported by a VICI grant (#453-12-001) from the Netherlands Organization for Scientific Research (NWO) and a starting grant from the European Research Council (ERC_StG2012_313749) awarded to Karin Roelofs.
Keywords: Defensive Reactions, Anxiety Disorders, Parasympathetic-Sympathetic Balance, Longitudinal Stress Research, Symptom Development

31. The PAG in Conditioned Respiratory Threat, Relevance for Anxiety Disorders

Kyle Pattinson[1]

[1]University of Oxford

Background: Breathlessness is a key feature of panic disorder, respiratory and cardiac disease. The columnar structure of the PAG is recognised from animal work. Here we investigate how anxiety modulates breathlessness-related activity in the individual PAG columns in humans.
Methods: Healthy subjects were conditioned to associate visual cues with impending breathlessness. They subsequently underwent 7T FMRI during anticipation and induction of experimental breathlessness. Study 1: PAG optimized scanning (1.5x1.5x1.5mm resolution, limited field of view); Study 2, whole brain, 2x2x2mm). Patients with chronic obstructive pulmonary disease (COPD) (n=41) were presented with breathlessness-related word cues during 3T FMRI. Statistical analysis used FEAT, cluster corrected, threshold Z>2.3.
Results: Study 1: Activity was observed in the ventrolateral PAG (vlPAG) during anticipation, and in the lateral PAG (lPAG) during breathlessness. Study 2: The lPAG demonstrated resting functional connectivity with cortical sensorimotor areas, conducive to facilitating fight/flight responses, and increased connectivity with the amygdala during

breathlessness that scaled with anxiety scores. The vlPAG showed fronto-limbic connectivity at rest, during anticipation reduced functional connectivity was seen to lPAG and motor structures, conducive to freezing behaviours. During breathlessness connectivity between vlPAG and the insula scaled with anxiety scores. COPD patients demonstrated activity in the vlPAG associated with breathlessness-related word cues.
Conclusions: We have revealed spatially and temporally distinct functions within the PAG during respiratory threat that are modulated by anxiety, findings relevant for the understanding of breathlessness in panic disorder. We propose that lPAG is involved with sensorimotor responses to breathlessness, while vlPAG operates within the threat perception network for impending breathlessness.
Supported By: Medical Research Council (UK), JABBS Foundation
Keywords: BOLD fMRI, Panic Disorder, Brain Networks

32. Interoceptive Gating of Anxiety and Fear, a Novel Target for Anxiety Treatment

Hugo Critchley[1], Jessica Eccles[1], Cassandra Gould van Praag[1], David Watson[1], and Sarah Garfinkel[1]

[1]Brighton and Sussex Medical School

Background: Arterial baroreceptors inform the brain about cardiovascular arousal, signaling the strength and rate of heartbeats. We showed that these signals selectively enhance processing of fear and threat, interacting with individual differences in anxiety and interoceptive sensitivity. Here, we examine their impact on fear learning with clinical relevance to anxiety disorders.
Methods: We used classical conditioning to quantify human fear learning of brief (100ms) CS+ and CS- stimuli presented at systole (during arterial baroreceptors activation) against stimuli presented at diastole (N=40 healthy volunteers). Results are interpreted in the context of neuroimaging findings and studies of anxiety patients.
Results: Cardiac signals at systole influence fear conditioning by 1) generalizing fear responses (measured electrodermally during early acquisition as a main effect of cardiac timing in absence of CS effect $F(1, 38)=7.47$, $p=0.009$); and 2) enhancing fear learning (measured in later acquisition as CS by cardiac timing interaction, $F(1, 38)=4.06$, $p<0.05$). 3) These signals also 3) represent a context in which fear memories are maintained or extinguished (heart timing contingency was switched at extinction for half the participants yielding a significant 3-way interaction [$F(1, 38)=7.25$, $p=0.01$). 4) These effects are amplified in people with high trait anxiety (median split on trait anxiety, $F(1, 38)=6.87$, $p=0.013$).
Conclusions: Our findings show integration of interoceptive cardiac signals with the formation, retention and extinction emotional memories. We have now also shown how this effect may be integrated with computerized exposure therapy in anxiety treatment, and relate to embodied mechanisms involving PAG circuitry that can be targeted pharmacologically.

Supported By: European Research Council FP7 AdG 324150 CCFIB to HDC
Philanthropic donation from the Dr. Mortimer and Theresa Sackler Foundation
Keywords: Anxiety, Autonomic Nervous System, Fear, Interoception, Intervention

SYMPOSIUM
Dissecting Psychiatric Heterogeneity With Machine Learning and Brain Imaging to Predict Outcomes in Adolescents and Young Adults

12:30 p.m. - 2:30 p.m.
Chair: Daniel Wolf
Co-Chair: Nikolaos Koutsouleris

33. Discovering Linked Dimensions of Psychopathology and Functional Connectivity

Cedric Xia[1], Zongming Ma[1], Rastko Ciric[1], Shi Gu[1], Richard Betzel[1], Antonia Kaczkurkin[1], Monica Calkins[1], Phillip Cook[1], Angel Garcia de La Garza[1], Simon Vandekar[1], Tyler Moore[1], David Roalf[1], Kosha Ruparel[1], Daniel Wolf[1], Christos Davatzikos[1], Ruben Gur[1], Raquel Gur[1], Danielle Bassett[1], and **Theodore Satterthwaite**[2]

[1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: It is increasingly realized that neurobiological abnormalities associated with mental illnesses do not map cleanly to diagnostic categories used in clinical practice. This suggests common mechanisms of circuit-level abnormalities that cross clinical diagnostic boundaries.
Methods: Here we sought to identify brain-based dimensions of psychopathology using sparse Canonical Correlation Analysis (sCCA) in a sample of nearly 1000 youth imaged as part of the Philadelphia Neurodevelopmental Cohort. These participants were divided into a discovery sample (n=663) and an independent replication sample (n=336). To find relationships between functional network connectivity and psychopathology data, we used sCCA, which aims to simultaneously find linear combinations of variables in each dataset that are maximally correlated with each other, with elastic net (L1+L2) regularization to achieve sparsity. Significance was assessed using permutation testing; multiple comparisons were controlled using the False Discovery Rate. Feature significance was assessed using bootstrapped confidence intervals.
Results: We found that three dimensions of psychopathology— mood ($r=0.70$, $pFdr<0.001$), psychosis ($r=0.71$, $pFdr<0.001$), fear ($r=0.68$, $pFdr<0.01$)— were highly associated with distinct patterns of functional dysconnectivity. Loss of network segregation between the default mode network and executive networks emerged as a common feature across all dimensions. Connectivity patterns linked to mood and psychosis became more prominent with development, and significant sex differences were present for connectivity patterns related to mood and fear (all $pFdr<0.001$).

Critically, mood and fear dimensions were replicated in the replication dataset.
Conclusions: These results delineate connectivity-guided dimensions of psychopathology that cross clinical diagnostic categories, which could serve as a foundation for developing network-based biomarkers in psychiatry.
Supported By: R01MH107703 (TDS), R01MH112847, (RTS TDS), R21MH106799 (DSB & TDS), R01MH107235 (RCG), and R01EB022573 (CD).
Keywords: Functional Connectivity, Machine Learning, Adolescence, Dimensional, Neuroimaging

34. Predicting Functional Disability in Young Adults at Risk for Psychosis and Relapsing Depression Using Multi-Site, Multi-Modal Machine Learning: Results From the European PRONIA Project

Nikolaos Koutsouleris[1]

[1]Ludwig-Maximilians-Uinversity

Background: Clinical high-risk (CHR) states for psychosis and relapsing depression confer high odds for enduring functional disability but considerable heterogeneity characterizes this crucial outcome dimension. So far, early intervention strategies lack prognostic models that could reliably deconvolve this heterogeneity at the single-subject level.
Methods: Therefore, we trained and validated clinical, imaging-based, and combined machine learning models to predict the 1-year social functioning outcomes in 116 CHR persons and 109 patients with Recent-Onset Depression (ROD) followed in PRONIA (www.pronia.eu), a longitudinal study involving 7 European sites. Furthermore, we explored the prognostic relevance of the models across different functioning domains and benchmarked their performance against the prognostic evaluations of our raters.
Results: Outcomes could be estimated in CHR/ROD subjects with a cross-validated balanced accuracy of 80.1%/62.3% using clinical, 76.2%/68.0% using neuroanatomical, and 85.4%/62.7% using combined machine learning. Raters forecasted the CHR/ROD subjects' outcomes correctly in 71.6%/63.2% of cases. CHR subjects' outcomes were predicted by lower social functioning prior to study inclusion, and by medial prefrontal, orbitofrontal, and temporo-parieto-occipital gray matter volume (GMV) reductions, as well as cerebellar and dorsolateral prefrontal GMV increments. The prognostic signatures in the ROD group involved low current and past social functioning as well as medio-temporal GMV reductions and prefrontal-perisylvian GMV increments.
Conclusions: In summary, machine learning may provide effective neuromarkers to identify persons at risk of functional disability due to early psychotic and depressive syndromes. Embedded in clinical research and care, these markers could inform the development and administration of preventative interventions aiming at improving functional deficits caused by these conditions.
Supported By: EU-FP7
Keywords: Clinical High-Risk States for Psychosis, Recent-Onset Depression, Social Functioning, Outcome Heterogeneity, Multimodal Prognostic Modelling

35. Heterogeneity in First Episode Psychosis, and Prediction of Progression

Paola Dazzan[1]

[1]Institute of Psychiatry Psychology and Neuroscience

Background: Difficulties in the prediction of outcome after the onset of psychosis are linked to the high clinical and biological heterogeneity of this disorder. Subtle and diffuse alterations in brain structure are already present at the onset, but seem to characterise those patients with particularly poor outcome. Large multi-centre MRI studies can provide the scale needed to identify the neuroimaging markers specifically associated with clinical outcomes.
Methods: We used Magnetic Resonance Imaging in multiple datasets of patients with first episode psychosis (n=410), and followed up to evaluate 1-month to 6-year clinical outcome. We used machine learning approaches in both single and combined datasets, using measures of volume and morphology (cortical thickness, surface area, gyrification).
Results: In the individual datasets, smaller volumes of frontal and temporal areas predicted illness episodes over 6 years with significant accuracy (70% correctly classified; p=0.005). Combining data from multiple centres, the accuracy in predicting long-term clinical outcome decreased to just above chance. Interestingly, accuracy in classification improved when biological heterogeneity was reduced, for example by restricting analyses to male patients only. Furthermore, the prediction of treatment response at 1-month showed that accuracy was affected by imbalances in the number of subjects included in each outcome class, with better classification achieved when number of subjects with poor or good 1-month treatment response was almost equal.
Conclusions: Combining multi-center MRI data to create a well performing classification model for psychosis is possible, but each center should contribute a sample either large or homogeneous enough to first allow accurate classification within the single-center.
Supported By: MRC, NARSAD, EU
Keywords: Treatment Response, MRI, Psychosis, Outcome, Brain Structure

36. Quantifying Anatomical and Functional Heterogeneity in Big Datasets, Using Machine Learning Methods Towards a Dimensional Neuroimaging Framework

Christos Davatzikos[1]

[1]University of Pennsylvania

Background: Neuropsychiatric disorders are characterized by highly heterogeneous and frequently overlapping clinical phenotypes. Understanding the neurobiological underpinnings of these clinical symptoms has been central in neuropsychiatric research and has been largely facilitated by MRI and associated analytical methods that have found reproducible neuroanatomical abnormalities. Multivariate machine learning approaches have been quite successful in capturing complex imaging patterns that have diagnostic and predictive value.

However, the neuroanatomical heterogeneity in neuropsychiatric disorders is high, therefore attempting to find a unique neuroanatomical signature of a complex neuropsychiatric disorder using commonly used current techniques is hampered by such heterogeneity. Personalized disease treatment calls for fine quantification of heterogeneity and for more precise placement of each individual patient into a multidimensional spectrum of neuroanatomical alterations found in neuropsychiatric disorders.

Methods: We present semi-supervised machine learning frameworks, which allow us to characterize differences between populations, such as patients and controls, in a dimensional way that captures disease heterogeneity. We present results from studies of schizophrenia, brain development, and aging.

Results: We elucidate neuroanatomical heterogeneity in schizophrenia, as well as structural and functional heterogeneity in brain aging trajectories that deviate from typical brain aging. Associations of neuroimaging dimensions with cognitive and clinical measures are also discussed. The application of these methods in a large consortium of pooled cohorts from 10 sites is presented, including adults with chronic schizophrenia-spectrum (non-affective) psychotic disorders (n=749), individuals with first-episode psychosis (n=665), and matched healthy controls (N=1,483).

Conclusions: In this context, we discuss challenges and solutions pertaining to inter-study heterogeneity of image quality and characteristics.

Supported By: R01MH112070

Keywords: Big Data Analysis, Machine Learning, Disease Heterogeneity, Neuroimaging

SYMPOSIUM
Biomarker Candidates and New Therapeutics for PTSD, TBI, and Pain - Accelerating Bench to Bedside Translation

12:30 p.m. - 2:30 p.m.
Chair: Chris Marx
Co-Chair: Murray Stein

37. Inflammatory Markers and Other Biomarker Candidates in PTSD: INTRuST Consortium Biorepository Findings

Mercedes Szpunar[1], Ariel Lang[2], Christine Marx[3], and Murray Stein[4], INTRuST Clinical Consortium

[1]UCSD School of Medicine, [2]VA San Diego Healthcare System, UCSD, [3]Duke University Medical Center/Durham VA, [4]University of California, San Diego

Background: Accumulating evidence suggests that inflammatory markers and other biomarker candidates (such as biomarkers of metabolism, amino acids, and acylcarnitines) may be relevant to the development of posttraumatic stress disorder (PTSD). Inflammatory markers of interest include C-reactive protein (CRP) and proinflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8). We thus quantified these analytes in serum samples from participants in the Injury and Traumatic Stress (INTRuST) Consortium Biorepository.

Methods: Participants with PTSD and a history of traumatic brain injury (TBI) (n=99) and control participants (n=194) were enrolled in the INTRuST Consortium (total n=293). Inflammatory markers, amino acids, acylcarnitines, and markers of metabolism were quantified in serum samples using mass spectrometry, immunoassay, and other techniques. Analytes that were selected by all 4 statistical analysis approaches are reported below (Wilcoxon Rank Sum Test; Partial Least Squares, Discriminant Analysis; Significance Analysis of Microarray; and Empirical Bayesian Analysis of Microarray). To assess potential relationships with PTSD Symptom Checklist (PCL) scores, data were log transformed and linear regression analyses were conducted, adjusting for age.

Results: The following analytes were significantly associated with PTSD ($p<0.05$ in all four of the above statistical analysis approaches for each analyte): IL-6, IL-8, glutamine/glutamate, ornithine, and the C16 acylcarnitine derivative. In the linear regression analyses, CRP, IL-6, IL-8, non-esterified fatty acids, and glutamate/glutamine were positively associated with PTSD symptoms, as assessed by the PCL ($p<0.05$). The C3 and C5 acylcarnitines derivatives were inversely associated with the PCL ($p<0.05$).

Conclusions: Inflammatory markers, amino acids, acylcarnitines, and biomarkers of metabolism are related to PTSD and its symptomatology, as assessed by the PCL. Identifying biomarker signatures could enhance diagnosis assessment and lead to new intervention strategies.

Supported By: DoD W81XWH08-2-0159; NIH R25 MH 101072-4

Keywords: Inflammatory Markers, Amino Acids, Acylcarnitines, PTSD

38. GABAergic Neurosteroids in Cerebrospinal Fluid are Negatively Associated With PTSD Severity in Men

Ann Rasmusson[1], Matthew King[2], Suzanne Pineles[3], Ivan Valovski[4], Kristin Gregor[5], Erica Scioli-Salter[5], Mohamed Hamouda[4], Yael Nillni[3], and Graziano Pinna[6]

[1]Boston University School of Medicine, [2]National Center for PTSD, [3]National Center for PTSD, Boston University School of Medicine, [4]VA Boston Healthcare System, Harvard Medical School, [5]VA Boston Healthcare System, Boston University School of Medicine, [6]University of Illinois at Chicago

Background: Previous research demonstrated decreases in the GABAergic neurosteroids allopregnanolone and pregnanolone (together termed ALLO) in the cerebrospinal fluid (CSF) of women with PTSD, which correlated with PTSD re-experiencing and depression symptoms. A low ratio of ALLO to 5-alpha-dihydroprogesterone (a steroid precursor), indicated a block in ALLO synthesis catalyzed by the 3-alpha-hydroxysteroid dehydrogenase enzyme. Recent research in women with PTSD confirmed the site of this block in plasma, as well as a PTSD-related deficit in the capacity to increase ALLO synthesis during stress.

Methods: Lumbar punctures (LPs) were performed in trauma-exposed, fasting, unmedicated, tobacco-free men with (n=13) and without (n=15) PTSD. Neuroactive steroids in CSF and plasma were quantified by gas chromatography/mass spectrometry after separation by high performance liquid chromatography.
Results: In the men with PTSD, CSF ALLO levels correlated negatively with total Clinician-Administered PTSD Scale (CAPS-IV) scores (Spearman r =-0.63; p=0.03) and Simms dysphoria cluster scores (r=-0.66, p=0.02). The ratio of ALLO to DHEA, which allosterically antagonizes and facilitates, respectively, GABA-A and N-methyl-D-aspartate receptors, correlated more strongly with Simms dysphoria cluster scores (r=-0.84, p=0.0006). A PTSD-related decrease in the ratio of 5-alpha-dihydroprogesterone to progesterone indicated a block in ALLO synthesis at the 5-alpha-reductase step (64.1 vs. 25.8, 95% confidence interval [-0.42; 76.9], p=0.05).
Conclusions: Blocks in conversion of progesterone to ALLO manifest in both women and men with PTSD, and account for substantial variance in PTSD and PTSD-related depression/dysphoria symptom severity. The enzyme site at which ALLO synthesis is blocked in PTSD appears to vary by sex, however, suggesting opportunities for development of sex-specific PTSD treatments.
Supported By: NIMH and the VA National Center for PTSD
Keywords: PTSD - Posttraumatic Stress Disorder, Allopregnanolone, Cerebrospinal Fluid, Male

39. Biomarkers and New Therapeutics in PTSD and TBI: Neurosteroid Signatures to Randomized Controlled Trials

Chris Marx[1]

[1]Duke University Medical Center/Durham VA Medical Center

Background: Neurosteroids are enriched in brain and exhibit pleiotropic actions. Allopregnanolone (ALLO) is a downstream metabolite of pregnenolone (PREG) that has neuroprotective, neurotrophic, and neurogenesis-enhancing properties, and also increases myelination.
Methods: We thus quantified neurosteroids in serum samples from participants with PTSD and control subjects in two independent cohorts - the INjury and TRaumatic STress (INTRuST) Biorepository Cohort and the VA Mid-Atlantic MIRECC Post-Deployment Mental Health (PDMH) Study. We also conducted a randomized controlled trial (RCT) with a neurosteroid intervention in Iraq/Afghanistan-era veterans with mild TBI (treatment duration 8 weeks). Diffusion tensor imaging (DTI) at baseline and post-treatment was conducted in a subset of participants.
Results: In the INTRuST cohort, ALLO levels were decreased in male participants with PTSD (n=107) compared to control subjects (n=103), p=0.0007; ALLO levels were also reduced in the PDMH Study in male participants with PTSD (n=133) compared to controls (n=347); p=0.012 (Box-Cox regression analyses; age and smoking as pre-determined covariates). In the RCT, 53 participants were randomized to PREG or placebo; 44 participants had at least one post-randomization assessment and were thus included in the modified intent-to-treat analysis. PREG significantly out-performed placebo for the primary behavioral endpoint (Criterion D of the CAPS), $p<0.05$. In the pilot neuroimaging component, treatment with PREG (n=13) but not placebo (n=6) enhanced fractional anisotropy on DTI compared to baseline.
Conclusions: ALLO levels were significantly decreased in male participants with PTSD in both the INTRuST and MIRECC PDMH cohorts. Treatment with PREG outperformed placebo for the primary behavioral endpoint, and may enhance white matter integrity.
Supported By: VA Merit Review, VA Mid-Atlantic MIRECC
Keywords: TBI, Neurosteroid, Novel Intervention, Biomarker, Diffusion Tensor Imaging (DTI)

40. From Biomarker Candidates to a New Therapeutic Intervention for Pain

Jennifer Naylor[1]

[1]Durham VA Medical Center/Duke University Medical Center

Background: Chronic low back pain (CLBP) is highly prevalent in Iraq/Afghanistan-era Veterans, and diagnoses of this potentially disabling condition are increasing in the VA at a rate of about 5% each year. The effective treatment of CLBP symptoms is thus of paramount importance, and new therapeutic agents that are non-habit forming, safe, and efficacious are urgently needed. Our prior investigations examining neurosteroids as biomarker candidates of self-reported pain symptoms suggest that dysregulation of these molecules may contribute to the pathophysiology of pain symptoms (Kilts et al., 2010, Naylor et al 2016), and that ameliorating these deficits could be clinically therapeutic.
Methods: We conducted a randomized controlled trial (RCT) with an adjunctive neurosteroid intervention (pregnenolone) in a cohort of 92 veterans with low back pain (4-week duration of treatment with pregnenolone or placebo). The primary endpoint was the mean weekly pain rating scales averaged from daily diaries (numerical rating scale of 0-10). Neurosteroids and other small molecules were quantified in serum samples at multiple time points during the 4-week treatment with pregnenolone or placebo.
Results: Pregnenolone (n=41) significantly out-performed placebo (n=42) in reducing pain severity ratings, the primary endpoint for this study (p=0.006). Additionally, low back pain intensity ratings were inversely associated with serum neurosteroid levels, suggesting that deficits in these molecules (some of which have analgesic properties) could potentially contribute to pain symptoms in this cohort.
Conclusions: Treatment with pregnenolone could represent a promising new intervention for chronic low back pain that is safe, efficacious, and non habit-forming. Quantifying serum neurosteroid levels holds promise for the prediction of therapeutic response.
Supported By: VA Rehabilitation Research & Development Career Development Award 1IK2RX000908
Keywords: Neurosteroids, Clinical Trial, Pain

SYMPOSIUM
Accelerated Aging in Depression: From Physiological Aging to Brain Aging

12:30 p.m. - 2:30 p.m.
Chair: Brenda Penninx
Co-Chair: Lianne Schmaal

41. Telomere Length, Epigenetic Aging and Depression in the Netherlands Study of Depression and Anxiety (NESDA)

Laura Han[1], Josine Verhoeven[1], Moji Aghajani[2], Shaunna Clark[3], Mohammad Hattab[3], Andrey Shabalin[3], Min Zhao[3], Gaurav Kumar[3], Robin Chan[3], Lin Ying Xie[3], Yuri Milaneschi[1], Rick Jansen[1], Karolina Aberg[3], Edwin van den Oord[3], and Brenda Penninx[1]

[1]VU University Medical Center, [2]VU University Amsterdam, [3]Center for Biomarker Research and Precision Medicine, School of Pharmacy, Virginia Commonwealth University

Background: Patients with depression show increased risk of developing aging-related diseases. General literature shows accelerated aging in depression by shorter telomere length (TL), also found in NESDA (Cohen's d=0.12). Here, we sought to confirm accelerated biological aging in depression using a novel method based on DNA methylation (DNAm) patterns, and whether these patterns impact disease characteristics.
Methods: DNAm_age was estimated using DNAm levels of all CpG sites in blood of 1130 subjects (811 depressed). By regressing estimated DNAm_age on age, the methylation aging pattern was translated into one outcome: "DNAm_age_residuals". Diagnosis and clinical characteristics were assessed with questionnaires and psychiatric interviews. Analyses were adjusted for sociodemographics, lifestyle, and health status. A pathway enrichment analysis was conducted using ConsensusPathDB to gain insight in the biological processes underlying DNAm_age_residuals.
Results: Higher DNAm_age_residuals were observed in depressed patients compared to controls (P=0.008, Cohen's d=0.18), with a dose-effect with increasing symptom severity in the overall sample (P=0.001). Within patients, DNAm_age_residuals were positively associated with childhood trauma scores (P=0.02). Post-hoc analyses between TL and DNAm_age_residuals showed non-significant relationships, and results remained significant independent from TL. Top significantly enriched Gene Ontology terms included neuronal processes such as neurogenesis and neuron differentiation.
Conclusions: Our finding of accelerated epigenetic aging in depressed patients is in line with previous TL findings. While both suggest an explanation for increased risk of mortality and aging-related diseases in MDD, they likely independently track different aspects of biological aging. Further research is needed to examine longitudinal and causal relationships between age-associated alterations in TL, DNAm_age, and depression.

Supported By: This work was supported by grant R01MH099110 from the National Institute of Mental Health.
Keywords: Aging, Epigenetics, Depression, Telomere Length

42. Epigenetic Age Acceleration in Depression

Andrew McIntosh[1], Riccardo Marioni[1], Heather Whalley[1], Kathryn Evans[1], and Chris Haley[1]

[1]University of Edinburgh

Background: Major Depression (MDD), neuroticism and psychological distress have each been associated with an increased risk of several diseases commonly associated with ageing. In the current study, we sought to identify which of these traits was associated with methylation age acceleration, and if any methylation age association with MDD or distress survive correction for neuroticism.
Methods: We conducted assessments of DNA methylation age in Generation Scotland (N=22,000 individuals), a family and population-based cohort from Scotland. DNA methylation was assessed genome wide using the Illumina EPIC array in 5000 individuals, of whom 500 were also assessed longitudinally, accelerated biological ageing was calculated using the Horvath clock
Results: Associations were found between methylation age acceleration, MDD and psychological distress (β=0.0275, p=0.023 equivalent to 0.20 years). These differences were not due to differences in cell counts, smoking or alcohol misuse. Increased body mass index in depressed individuals appeared to account for a proportion of the observed differences (partial mediation between EAA and depression through BMI (Z=3.026-3.8410; p=0.003 to <0.001, proportion of effect size mediated ~14%)).
Conclusions: These findings suggest that accelerated biological ageing is associated MDD and psychological distress, and later analyses from this dataset will seek to determine the directional relationship, and specifically whether MDD is leading to ageing acceleration, or whether accelerated ageing is increasing the likelihood to developing MDD.
Supported By: Wellcome Trust 104036/Z/14/Z
Keywords: Depression, Age, Clinical Comorbidities, Epigenetics

43. Accelerated Aging in Depression: From Physiological Aging to Brain Aging

Hans Grabe[1], Sandra Van der Auwera[1], Stefan Frenzel[1], Uwe Völker[1], Henry Völzke[1], and Mohamad Habes[2]

[1]University Medicine Greifswald, [2]University of Pennsylvania

Background: Brain aging refers to the age-depended atrophy of large parts of the brain. However, there is considerable difference in the speed of brain aging between different subjects. Based on machine learning algorithms we have determined the individual deviation from the mean regression over the population. We aim at exploring how depressive disorders, childhood traumatization and polygenetic risk scores (PRS)

impact on brain age. PRS (Van der Auwera et al. Biol Psychiatry, 2015) are based on the recent results from genome-wide association analyses (GWAS) of schizophrenia, educational attainment (EA) and body-mass index (BMI).
Methods: We used epidemiological data from the Study of Health in Pomerania (SHIP) in Germany. MRI scans (N>2500) and genetic data (N>3000) are available from the general population (age 35-85). Clinical interviews were performed in addition to self-rating questionnaires (Childhood Trauma Questionnaire, Beck Depression Inventory II).
Results: BDI-II was positively associated with accelerated brain aging (N=2510, p=0.00027). Childhood trauma showed a slightly negative association with less brain aging (N=2505, 0=0.033). Higher BMI and smoking were associated with accelerated brain aging (N=2707, p=2.3E-5 and N=2717, p=3.7E-5). Interactions: Subjects with higher PRS for schizophrenia plus childhood abuse showed more age-specific brain atrophy (N=1617, p=0.025). Moreover, subjects with a lower genetic score for EA plus current depression showed more age-specific brain atrophy (N=1653, p=0.0089).
Conclusions: Depressive symptoms are associated with higher brain age. This effect is increased by the genetic risk for low educational attainment. Childhood abuse interacts with risk SNPs related to schizophrenia. Sensitivity and replication analyses are under way.
Supported By: German Research Foundation, BMBF
Keywords: Depressive Symptoms, Genetics, Brain Age, Polygenic Risk Score, Childhood Trauma

44. Brain Aging in Major Depressive Disorder: Results From the ENIGMA MDD Consortium

Lianne Schmaal[1], Laura Han[2], Richard Dinga[2], Paul Thompson[3], Dick Veltman[2], and Brenda Penninx[2]

[1]Orygen, The National Centre of Excellence for Youth Mental Health, [2]VU University Medical Center, [3]Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging & Informatics, Keck School of Medicine of the University of Southern California

Background: Major Depressive Disorder has been associated with accelerated biological aging. From a brain perspective, normal aging is associated with significant loss of grey matter and depression may have an accelerating effect on age-related brain atrophy. Here, data on brain aging in MDD from the ENIGMA MDD Working Group will be presented.
Methods: A normative model of brain-based age was developed in 4708 healthy controls by applying a Gaussian Process Regression analysis with 10-fold cross-validation to estimate chronological age from structural MRI scans, separately for males and females. This model was then applied to 2924 MDD individuals to predict their brain-based age. Accelerated brain aging was measured as the difference between predicted brain-based age and actual chronological age (brain age gap).
Results: The brain age model explained 92% and 93% of the age variance in female and male healthy controls, respectively. The mean absolute error (MAE) was 6.79 years in females and 6.60 in males. Application of the model to MDD patients showed a mean brain age gap of 0.75 years in females (MAE=6.82) and 0.64 in males (MAE=6.68), which were significantly lower than brain age gap estimates in healthy controls in both females (F(1,4379)=6.10,P=0.01) and males (F(1,3166)=4.07,P=0.04). Our preliminary analysis also showed greater brain age gap associations with various clinical characteristics.
Conclusions: We found preliminary evidence for accelerated brain aging in MDD, however, the brains of patients were estimated to be only <1 years older than healthy controls. The impact of different methods, feature selection and potential confounding effects will also be discussed.
Supported By: NIH Big Data to Knowledge (BD2K) award (U54 EB020403)
Keywords: Depression, Brain Aging, Neuroimaging, Structural MRI

SYMPOSIUM
On the Computational Structure of Mood and Anxiety Disorders
12:30 p.m. - 2:30 p.m.
Chair: Quentin Huys

45. The Interaction Between Mood and Value

Daniel Bennett[1] and **Yael Niv**[1]

[1]Princeton University

Background: Previous work suggests that in some individuals there exists a positive feedback relationship between mood and valuation – unexpected rewards elevate mood, and in a better mood, rewards seem even better than they would otherwise be (and vice versa for bad moods and losses). Such positive feedback constitutes a principal cause of instability, suggesting a potential explanation for mood instability in disorders like cyclothymia and bipolar disorder.
Methods: We test three groups of participants (bipolar disorder, major depression, and age-matched healthy controls) on a behavioral task that allows us to quantify the strength of each participant's positive feedback between mood and evaluation. Briefly, participants learn about different reward sources, and then choose between equally-rewarding sources that were encountered before and after a mood manipulation phase. Using a computational model, we quantify for each individual the strength of the positive feedback between mood and valuation.
Results: Our previous results, replicated in two experiments (N=31 & N=33), indicated that self-reported mood instability is associated with a positive-feedback effect of mood on the evaluation of outcomes. Data collection from patients is still ongoing, but we expect the current task to show that patients suffering from bipolar disorder display a stronger positive feedback relationship between mood and valuation than patients suffering from depression and healthy participants.
Conclusions: Our results will provide a behavioral test that can quantify the tendency for patients to suffer from mood instability. In the long run, such a test can be used both for diagnosis and for tracking symptoms throughout treatment.

Supported By: NIDA grant 1DA042065
Keywords: Mood Instability, Reinforcement Learning, Computational Psychiatry

46. Characterising Algorithms for Threat Learning

Dominik Bach[1]

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Background: Anxiety disorders often entail exaggerated threat prediction. Here, we address computational algorithms for learning threat prediction, using discriminative delay fear conditioning in healthy humans. Fear conditioning is suggested to implement a prediction error-based reinforcement learning (PERL) algorithm, but more general theories of brain function imply probabilistic computations.
Methods: In three experiments (overall N = 68), we recorded skin conductance (SCR) and pupil size responses (PSR). We used random-effects Bayesian model selection of maximum-likelihood fits. In a fMRI study (N = 22) with 4 CS, we examined neural representations of prediction error signals in an axiomatic approach.
Results: Trial-by-trial SCR and PSR trajectories over 160 trials were best described by a probabilistic learning model, while extant PERL models provided a quantitatively and qualitatively worse fit. The best-fitting probabilistic learning algorithm maps a linear combination of threat prediction and its uncertainty onto SCR, and threat prediction onto PSR (protected exceedance probabilities 0.99, 0.85, 0,98, respectively for SCR, and 0.68 for PSR). Using fMRI, we found no neural signals fulfilling necessary conditions for representation of prediction errors. Quantities from the probabilistic learning model were represented in several brain regions ($p < .05$ FWE).
Conclusions: Overall, a probabilistic learning model provided a parsimonious description of the data, while we found no evidence that threat prediction learning relies on a PERL algorithm. These findings extend Bayesian brain theories to subcortical threat learning systems.
Supported By: Swiss National Science Foundation; Olga-Mayenfisch-Foundation
Keywords: Fear Conditioning, Computational Psychiatry, Bayesian Brain Theory, Reinforcement Learning

47. Computational Models of Effort-Based Choice in Patients With Major Depression and Schizophrenia

Jessica Cooper[1], Robin Nusslock[2], Michelle Craske[3], Richard Zinbarg[2], Iris Ka-Yi Chat[2], Deanna Barch[4], Felice Reddy[3], Michael Green[3], William Horan[3], and Michael Treadway[1]

[1]Emory University, [2]Northwestern University, [3]University of California, Los Angeles, [4]Washington University

Background: Effort-based decision-making (EBDM) tasks have been widely used to quantify motivation in depression and schizophrenia, showing similar results in both groups. Recent theoretical work posits that this behavior may be attributable to different mechanisms: reduced subjective value computations in major depression, and failed cognitive control in schizophrenia (i.e. failure to consider all available information).
Methods: We adapted a subjective value model of choice behavior to analyze data from the Effort Expenditure for Rewards Task (EEfRT) in a large transdiagnostic sample of young adults (N = 252) and patients with major depression, schizophrenia, and matched controls (N = 293).
Results: Our model correctly predicted 83% of choices. Effort-related reductions in subjective value correlated with depressive symptom severity ($p < .01$), and with positive affect when controlling for other symptoms ($p < .05$). Results indicate that individuals with depressive symptoms used reward, effort, and probability information to make choices in a similar manner to control participants, but with greater effort-related devaluation of rewards ($p < .05$). Alternately, patients with schizophrenia were more frequently better fit (lower BIC) by a simple model that does not incorporate available information ($X2 = 8.8$, $p<.01$). This subset of patients may account for previously-reported EBDM group differences in schizophrenia.
Conclusions: Consistent with prior theoretical work, the current research suggests that group-level reductions in effort-based choice in patients with mood disorders and schizophrenia reflect different mechanisms. Furthermore, this work suggests that group-level differences in EBDM in schizophrenia may be driven by a subset of patients that can be identified using modeling.
Supported By: National Institutes of Health (MH102355, MH108605)
Keywords: Motivation, Mood Disorders, Schizophrenia, Computational Psychiatry

48. A Computational Approach to Understanding Motivational Symptoms in Depression

Jonathan Roiser[1], Vincent Valton[1], Madeleine Payne[1], Anahit Mkrtchian[1], Stephen Pilling[1], and Peter Dayan[1]

[1]UCL

Background: Motivational symptoms of depression are debilitating and associated with poor clinical outcome, but the mechanisms underlying them are poorly understood. This talk will present data examining how a variety of cognitive components of reward processing (including reinforcement learning, valuation, willingness to engage in effort, exploration and value-based choice) relate to depressive symptoms, using a computational approach.
Methods: Results from two studies, including 250 participants (healthy volunteers, unmedicated depressed patients, first degree relatives and remitted depressed patients), will be presented. Participants completed several cognitive measures of motivation, and motivational symptoms were assessed through questionnaires. Data were analysed using a hierarchical computational approach, with model parameters estimated in a Bayesian framework using sampling.
Results: In a non-clinical study (N=90), general depressive symptoms were associated with a reduction in reward sensitivity ($P<0.001$), while anhedonia was related to a lack of willingness to engage in effortful responding ($P<0.05$). In

a clinical study (N=50 depressed patients, N=30 first-degree relatives, N=30 remitted patients, N=50 healthy volunteers), surprisingly, reward learning, risk aversion and loss aversion were largely unrelated to depressive symptoms, though there was a small increase in learning from worse-than-expected outcomes only in currently depressed individuals ($P<0.05$). In both studies motivational symptoms were associated with a lower degree of uncertainty-driven exploratory behaviour ($P<0.05$). Preliminary results from an experimental medicine study investigating the impact of L-DOPA administration on motivational processing in depression will also be presented.
Conclusions: These findings illuminate the cognitive mechanisms contributing to depressive symptoms relating to disrupted motivational processing.
Supported By: Wellcome Trust
Keywords: Depression, Amotivation, Computational Psychiatry, Reward, Dopamine

SYMPOSIUM
The Endocannabinoid System: Potential Biomarker and Novel Treatment Target for PTSD

3:00 p.m. - 5:00 p.m.
Chair: Adriana Feder
Co-Chair: Matthew Hill

49. Endocannabinoid System in Posttraumatic Stress Disorder (PTSD) Early After Traumatic Injury

Terri deRoon-Cassini[1], Samantha Chesney[2], and Cecilia Hillard[1]

[1]Medical College of Wisconsin, [2]Marquette University

Background: In the immediate aftermath of injury it is unclear who demonstrates risk for posttraumatic stress disorder (PTSD). Pre-clinical data suggests the endocannabinoid signaling system responds to stress and acts as a buffer after trauma. The purpose of the present study was: 1) evaluate the role of early circulating endocannabinoid (2-AG, AEA) functioning in 6-month PTSD, and 2) evaluate polymorphisms of the cannabinoid receptor type 1 (CB1) and fatty acid amide hydrolase (FAAH) genes to determine differential PTSD risk. Based on preclinical data, we hypothesized lower 2-AG and AEA acutely after injury would confer risk for PTSD.
Methods: This was a prospective longitudinal study with 278 participants hospitalized after traumatic injury. In-hospital and at 6 months subjects underwent: blood draw, assessment of PTSD symptom severity (PSS) and PTSD diagnosis. Independent sample t-tests were used to evaluate differences in circulating eCB levels based on 6month PTSD status. Analysis of Variance (ANOVA) was conducted to determine differences in risk for PTSD based on CB1 and FAAH polymorphisms.
Results: 2-AG ($p = .03$) and AEA ($p = .05$) were significantly higher acute after trauma in those with chronic PTSD. Elevated AEA was maintained by 6 months and remained significantly correlated with PSS in women only ($p < .001$). CB1 and FAAH polymorphisms suggest a genetic contribution to differences in risk for PTSD symptoms.
Conclusions: Counter to the pre-clinical literature, higher levels of acute 2-AG and AEA increase PTSD risk in the traumatically injured, suggesting a role for the endocannabinoid system early after trauma in psychological distress outcome.
Supported By: NIH/NIMH, R21 MH 102838-01 A1
Keywords: PTSD, Endocannabinoids, Trauma

50. Resilience and Endocannabinoid System Function in World Trade Center Responders

Adriana Feder[1], Matthew Hill[2], Olivia Diab[1], Chloe Hirschowitz[1], Rachel Yehuda[1], and Robert Pietrzak[3]

[1]Icahn School of Medicine at Mount Sinai, [2]University of Calgary, [3]Yale School of Medicine

Background: While preclinical studies have demonstrated a key role of the endocannabinoid (eCB) system in promoting stress resilience, little is known about eCB system function in resilient human trauma survivors. Understanding the neurobiology of resilience is critical for prevention and treatment.
Methods: A diverse sample of responders [n=199, 83% male, age=53.9 (SD=8.3)] involved in rescue and recovery work following the 9/11 World Trade Center (WTC) attacks was recruited from a larger health monitoring cohort and assessed with in-person interviews (CAPS) and self-report scales (STAI, Beck Depression Inventory-II) on average 14 years post-9/11; participants also completed blood sample collection to measure plasma 2-arachidonoylglycerol (2-AG) and anandamide (AEA) levels. WTC-related exposure severity was assessed on average three years post-9/11/01 (e.g., handled human remains, caught in the dust cloud) and operationalized as a total sum (range 0-10). Cluster analysis was employed to identify responder groups based on (1) WTC exposure severity and (2) current stress-related symptomatology (combined depressive, anxiety and WTC-related PTSD symptoms).
Results: Cluster analysis revealed three groups: Control (low WTC exposure/low symptoms, 44%), Resilient (high WTC exposure/low symptoms, 24%) and Distressed (high WTC exposure/high symptoms, 30%). After removing three outliers (2-AG levels > 3 SDs from group mean), ANCOVA (covariate=BMI) revealed a significant between-group difference in mean 2-AG levels: Resilient Z score=0.12, Low-Exposed Control=-0.11, Distressed=-0.22; p=0.038. In post-hoc analyses, plasma 2-AG level was significantly higher in the Resilient than the Distressed group (p=0.012). AEA levels did not differ.
Conclusions: Results suggest that 2-AG levels are linked to stress resilience in human trauma survivors.
Supported By: CDC-NIOSH U01 OH010407 and CDC-NIOSH U01 OH010986
Keywords: Biomarkers, Resilience, Endocannabinoids, World Trade Center Responders, Trauma Exposure

51. Investigating Endocannabinoid Mechanisms in Posttraumatic Stress Disorder: Neuroimaging Studies With the Novel Fatty Acid Amide Hydrolase Probe, [11C]CURB

Isabelle Boileau[1], Duncan Westwood[2], Donald Richardson[3], Shawn Rhind[4], Rachel F. Tyndale[5], Ruth Lanius[6], Richard Bazinet[7], Nancy J. Lobaugh[2], and Sylvain Houle[8]

[1]University of Toronto and CAMH, [2]Research Imaging Centre, Campbell Family Mental Health Research Institute, CAMH, University of Toronto, Institute of Medical Science, [3]Western University of Canada, [4]Defence Research and Development Canada, [5]Campbell Family Mental Health Research Institute, CAMH, University of Toronto, [6]University of Western Ontario, [7]University of Toronto, [8]Research Imaging Centre, Campbell Family Mental Health Research Institute, CAMH, University of Toronto

Background: Fatty Acid Amide Hydrolase (FAAH), the enzyme responsible for terminating endocannabinoid signaling, is believed to be a key modulator of fear-related circuitry and to be increased in post-traumatic stress disorder (PTSD). This enzyme and other components of the endocannabinoid system are drug targets for stress-related conditions.

We investigated the status of FAAH and peripheral levels of endocannabinoids 2-AG and anandamide (AEA) in PTSD and assessed whether FAAH modulates fear-related neural circuitry.

Methods: Healthy subjects (n = 30) and individuals with PTSD (n = 7) participated in a PET scan following injection of the FAAH probe [11C]CURB and completed a fMRI session during emotion processing. Blood was collected to measure AEA and 2-AG. [11C]CURB binding (estimated with a 2TCM-I) was investigated brain-wide using repeated measures ANOVAs. Relationship between [11C]CURB and BOLD in the amygdala were assessed with linear regressions.

Results: We find no evidence for elevated FAAH in brain ($p = 0.23$) or reduced peripheral levels of AEA in PTSD ($p = 0.3$). Instead we find that subjects with PTSD have significantly elevated 2-AG ($p = 0.02$). Furthermore, in healthy controls and individuals with PTSD we find a positive relationship between [11C]CURB binding in amygdala and BOLD during fearful face processing ($r = 0.71$; $p = 0.01$).

Conclusions: These are the first data on endocannabinoid metabolism in living brain of individuals with PTSD. The multimodal imaging data point to the role of the endocannabinoid system in fear processing. Confirmation of these findings in a larger sample may advance development of a new imaging biomarker.

Keywords: Positron Emission Tomography, PTSD - Posttraumatic Stress Disorder, BOLD fMRI, Cannabinoids

52. Cannabinoid Facilitation of Fear Extinction in Posttraumatic Stress Disorder

Christine Rabinak[1], Craig Peters[1], Farrah Elrahal[1], Mohammed Milad[2], Sheila Rauch[3], K. Luan Phan[2], and Mark Greenwald[1]

[1]Wayne State University, [2]University of Illinois at Chicago, [3]Emory University

Background: Recall of extinction learning depends on corticolimbic networks and patients with posttraumatic stress disorder (PTSD) show decreased activity in these regions and poor extinction recall. An acute dose of Δ9-tetrahydrocannabinol (THC), prior to fear extinction in healthy volunteers, facilitates extinction recall by increasing activation of vmPFC-HPC. However, direct tests of cannabinoid effects in PTSD patients have not yet been conducted.

Methods: This double-blind, placebo-controlled, randomized study uses a Pavlovian fear learning paradigm to examine the effect of THC (7.5mg) vs. placebo (PBO), administered prior to extinction learning, on brain activation (functional magnetic resonance imaging [fMRI]) and skin conductance (SCR) responses in 51 trauma-exposed adults with (n=20; PTSD) and without (n=31; trauma-exposed controls; TEC) PTSD and 20 non-exposed healthy controls (HCs), testing extinction recall 24 hours after extinction learning.

Results: PTSD patients who received PBO during fear extinction exhibited poor extinction recall as evidenced by increased SCRs to a conditioned stimulus (CS) that was previously extinguished (CS+E). In contrast, PTSD patients who received THC during fear extinction exhibited good extinction recall (significantly lower SCR), compared to PBO; $p = 0.02$) and increased hippocampal activation to the CS+E during recall of extinction learning ($p < 0.05$, FWE). There was no drug effect on extinction recall in either control group (TEC, HC; ps > 0.05).

Conclusions: These findings provide the first evidence that pharmacological enhancement of extinction recall is feasible in PTSD patients using cannabinoid system modulators. Ultimately, the cannabinoid system may serve as a promising target for innovative intervention strategies in PTSD.

Supported By: K01MH101123

Keywords: PTSD - Posttraumatic Stress Disorder, Dronabinol, Fear Extinction, Hippocampus

SYMPOSIUM
Neural and Computational Mechanisms Underlying Suicidal Behavior
3:00 p.m. - 5:00 p.m.
Chair: J. John Mann

53. Neurotransmitter and Neural Circuitry Correlates of Suicide Risk

J. John Mann[1], M. Elizabeth Sublette[2], Maria Oquendo[3], Todd Ogden[4], Francesca Zanderigo[2], Jeffrey Miller[5], and Hanga Galfalvy[2]

[1]NY State Psychiatric Institute, [2]New York State Psychiatric Institute, Columbia University Medical Center, [3]University of Pennsylvania, [4]Columbia University & New York State Psychiatric Institute, [5]Columbia University

Background: Suicide risk is related to a cluster of traits comprising its diathesis that include excessive pessimism or suicidal ideation, altered decision-making, impaired learning and problem solving and social distortions. Identifying the underlying neurotransmitter abnormalities and altered neural circuits can potentially provide biomarkers of risk or resilience and prevention or treatment targets.
Methods: Subjects with major depressive disorder (MDD) and a suicide attempt history, psychiatric controls and healthy volunteers underwent serotonin system PET scans quantifying 5-HT1A receptors. All subjects were medication-free at the time of scanning. Patients then were followed for up to two years to assess outcome in terms of suicidal ideation and behavior.
Results: 15/134 MDD subjects made a suicide attempt and two were fatal. elevated 5-HT1A autoreceptor binding predicted the lethality of subsequent suicide attempts. This relationship also existed for suicidal ideation up to one year after the PET scan and with suicide intent.
Conclusions: Altered serotonin function is related to risk of more lethal suicide attempts and this relationship is partly mediated by suicidal ideation and partly by suicide intent. Normalizing 5-HT1A autoreceptors is a treatment or prevention target in terms of depression-related suicidal behavior.
Supported By: NIMH
Keywords: Suicide Risk Factors, Suicidal Ideation, PET Imaging, Outcome Prediction

54. Decision Process Abnormalities in Suicide: From Psychological Theories to Neural Mechanisms

Alexandre Dombrovski[1], Vanessa Brown[1], and Katalin Szanto[1]

[1]University of Pittsburgh

Background: Psychological theories of suicide emphasize escape motivations, however recent studies of decision-making in attempted suicide find disturbances in appetitive behavior. Functional MRI augmented with computational modeling revealed that impaired decision-making in suicide attempters is paralleled by disrupted expected value signals in paralimbic cortical regions, particularly the ventromedial prefrontal cortex (vmPFC). Aiming to replicate these findings, we also sought to determine whether disrupted value signals were related to suicidal ideation vs. suicidal behavior.
Methods: This interim analysis of data from an ongoing study included 27 older (50+) depressed suicide attempters, 20 depressed suicide ideators, 20 non-suicidal depressed and 24 non-psychiatric controls. In the scanner, participants completed a 3-armed bandit task, with long-term reward value manipulated independently from current reward. Expected value (EV) signals were modeled using reinforcement learning.
Results: In the overall sample, EV signals were represented in a paralimbic network including the vmPFC and the middle/superior temporal gyrus (MTG/STG). While depression was associated with blunted value signals in the bilateral MTG/STG, suicidal ideation predicted heightened EV signals in the left MTG/STG, and suicide attempts were associated with heightened EV signals in the right intraparietal lobule ($p_{voxelwise}<0.005$, $k>100$).
Conclusions: The advantage of computational model-based fMRI in investigating decision-making in suicide is that it maps the latent process of learning, rather than merely registering responses to experimental conditions. Altered representations of expected value – putatively related to inability to consider deterrents and alternatives – were again associated with suicidal ideation and suicidal behavior, however regional and cognitive specificity of these abnormalities requires further investigation.
Supported By: R01MH100095
Keywords: Suicide, Decision Making, Reinforcement Learning, Ventromedial Prefrontal Cortex, Reward Learning

55. Using Structural Neuroimaging to Define Phenotypes of Suicidal Behavior

Fabrice Jollant[1], Gerd Wagner[2], Stéphane Richard-Devantoy[3], Stefanie Köhler[2], Karl-Jürgen Bär[2], Gustavo Turecki[3], and Fabricio Perreira[4]

[1]Paris-Descartes University, [2]Jena University Hospital, [3]McGill University, [4]Nîmes University Hospital

Background: The identification of brain markers of suicidal risk is highly expected. However, neuroimaging studies have yielded mixed results, possibly due to phenotypic heterogeneity.
Methods: Two independent samples of suicide attempters (total N=49), patient controls (N=60), and healthy controls (N=100) were scanned with magnetic resonance imaging. Groups were compared with FSL (non parametric tests, 5,000 permutations, corrected $p<0.05$). We then reviewed the literature and run a meta-analysis of structural neuroimaging studies (14 studies, N=693 individuals) comparing suicide attempters and patient controls with GingerALE (cluster-level inference $p<0.05$). Finally, we explored the contribution of two variables to phenotypic heterogeneity: A family history of suicide, and the use of a violent suicidal mean. Here, we included in analyses two groups of healthy first-degree relatives of suicide victims and depressed patients (N=32).
Results: When comparing suicide attempters and controls, very limited between-group difference was found in the two samples, and none in the meta-analysis. However, a family history of suicide was associated with reduced volume in bilateral temporal regions, right dorsolateral prefrontal cortex, and left putamen. Moreover, several of these clusters were found across the three groups. Use of a violent suicidal mean was associated with increased bilateral caudate volumes.
Conclusions: These results suggest the heritability of several structural brain alterations in relation to suicide risk transmission, and the role of the striatum in the choice of a violent suicidal method. Overall, they confirm the need to consider particular phenotypes, as opposed to suicidal acts in general, when studying the biology of suicidal behavior.
Supported By: American Foundation for Suicide Prevention-AFSP (# SRG-0- 10-302); Canadian Institutes for Health Research (CIHR).

Keywords: Suicide Attempts, Structural Magnetic Resonance Imaging, Phenotype, Meta-analysis

56. Connectomics-Based Functional Network Alterations in Patients With Suicidal Behavior

Gerd Wagner[1], Feliberto de la Cruz[1], Stefanie Köhler[1], Fabrice Jollant[2], and Karl-Jürgen Bär[1]

[1]Jena University Hospital, [2]Université Paris-Descartes

Background: Suicide is a growing public health problem worldwide. Understanding neurobiological factors associated with suicide may help to specifically address suicidal behavior in clinical practice.
Methods: Two independent samples of suicide attempters (SA; n=42), patient controls (n=43) and healthy controls (n=66) from Montreal and Jena as well as an additional sample of relatives of suicide victims (n=16) and depressed patients (n=16) were investigated with functional MRI in the resting-state condition. Graph theoretical analysis was performed to identify potential changes in network organization and its topologic properties, using 262 ROIs derived directly from established networks. Network-based statistic approach was used to examine group differences between functional connectivity matrices, while controlling for the multiple comparison problem.
Results: Significant differences ($p<0.05$) were detected in specific topological measures, i.e. in the assortativity, clustering coefficient as well as in the path length across several network densities, distinguishing depressed patients with SA from patients without SA as well as relatives of suicide victims from relatives of depressed patients. We also detected striking differences in the network organization with respect to modular composition. Network-based statistics revealed a specific network with altered connectivity in patients with SA and relatives of suicide victims.
Conclusions: This is the first study combining graph theoretical measures with the network-based statistic in suicide attempters from two independent samples and in relatives. Results suggest heritable alterations especially in the network resilience in vulnerable individuals independently from comorbid depression and antidepressant effects. Additionally, altered connectivity in a specific sub-network indicates its specific role in the pathology of suicidal behavior.
Keywords: Suicide Attempts, Resting State fMRI, Connectomics, Network Connectivity

SYMPOSIUM
Pediatric Mood Outcomes: Neural Function and Structure Telling the Story Today and in the Future
3:00 p.m. - 5:00 p.m.
Chair: Ellen Leibenluft

57. Unique Neural Associations With Pediatric Irritability During Frustration and Threat Orienting

Ellen Leibenluft[1], Wan-Ling Tseng[1], Katharina Kircanski[1], Argyris Stringaris[1], Kenneth Towbin[1], Daniel Pine[1], and Melissa Brotman[1]

[1]Emotion and Development Branch, NIMH

Background: Irritability, defined as increased proneness to anger relative to peers, is extremely common in youth, yet there are few evidence-based treatments. Elucidating the relevant circuitry dysfunction would facilitate the development of mechanism-based interventions. We have posited two core deficits in irritability: aberrant responses to frustration (i.e., blocked goal attainment) and aberrant approach responses to threat. We present data from two fMRI studies, a frustration task and a threat orienting task.
Methods: For both studies, phenotyping consisted of dimensional measures of parent- and child-reported irritability and anxiety, and parent-reported ADHD. Whole-brain corrected analyses identified findings unique to irritability and to anxiety, while covarying effects of ADHD. The frustration study included 195 youth (severe impairing irritability (DSM-5 DMDD, n=52), anxiety (n=42), and/or ADHD (n=40), and healthy volunteers (HV, n=61). This was a cued-attention orienting task with reward contingencies that were rigged to induce frustration. The threat orienting study included 197 youth (DMDD=54, anxiety=50, ADHD=37, HV=56). Bifactor modeling differentiated unique and shared effects of irritability and anxiety.
Results: For the frustration task, on trials where subjects performed the attention orienting task following frustration, irritability was positively associated with fronto-striatal activation (r's=.31-.39, p's<.05). When subjects attended away from threat, higher parent-reported irritability was associated with increased activity in the amygdala ROI ($t189=2.30$, $p=.022$), insula, caudate, and ventrolateral and dorsolateral prefrontal cortex ($ts189>4.15$, $ps<.001$). Higher anxiety was associated with decreased amygdala connectivity to cingulate and thalamus ($ts189<-4.19$, $ps<.001$).
Conclusions: Unique neural associations with irritability during frustration and threat orienting that could serve as potential biomarkers and treatment targets.
Supported By: This research was supported by the Intramural Research Program (IRP) of the National Institute of Mental Health, National Institutes of Health (NIMH/NIH), ZIAMH002786 (Leibenluft) and ZIAMH002781 (Pine), and was conducted under NIH Clinical Study Protocols 00-M-0021 and 01-M-0192 (ClinicalTrials.gov IDs: NCT00025935 and NCT00018057).
Keywords: Irritability, Frustration, Threat Processing, Pediatric Psychopathology

58. Neural and Behavioral Phenotypes in Children of Parents With Mood Disorders

Manpreet Singh[1], Melissa Packer[1], Alexander Onopa[1], Sara Leslie[1], Yevgeniya Zaiko[1], Danielle Wall[1], Alexis Staver[1], Elizabeth Weisman[1], and Owen Phillips[1]

[1]Stanford University School of Medicine

Background: We compared behavioral and limbic structural and functional neuroimaging markers among healthy youth offspring of parents with bipolar disorder (BD), with major depressive disorder (MDD), and with no psychopathology to

investigate neurobehavioral risk markers for developing mood disorders among these youth.
Methods: Healthy boys and girls ages 8 to 17 years who were at risk for either BD (n= 34) or MDD (n=49) or were healthy comparisons (HC) (n=42) based on parental history underwent amygdala seed-based resting state functional and structural MRI, diurnal cortisol, and family environment assessments to investigate early clues of neurobehavioral dysfunction that may precede mood disorder development.
Results: Whereas HC youth showed relative negative connectivity between the amygdala and precuneus and the amygdala and superior frontal gyrus at rest ($p<0.001$), children of parents with MDD and BD showed no such relation among these regions. We also found that youth at risk for MDD and BD had larger amygdala volumes, compared to HC offspring. HC offspring demonstrated a positive relation between amygdala volume and diurnal cortisol response that was not present in MDD risk and BD risk offspring ($p<0.05$). MDD and BD risk youth did not distinguish themselves along these markers at a stage of health ($p>0.05$).
Conclusions: Our findings suggest that a familial risk for mood disorders differentiates these youth from healthy comparison youth along neural and behavioral phenotypes even preceding mood disorder onset. These neurobehavioral phenotypes may potentiate susceptibility toward poor mood outcomes in youth at risk for mood disorders that may signal the need for early interventions.
Supported By: Stanford Child Health Research Institute, K23MH085919
Keywords: Risk for Mood Disorders, Amygdala, Family History, Neural Networks

59. Neural Markers of Treatment Effects and Response in First-Episode Manic Youth

Melissa DelBello[1], Wenjing Zhang[2], L. Rodrigo Patino[3], Jeffrey Strawn[1], Jeffrey Welge[1], Christina Klein[1], Thomas Blom[1], Su Lui[2], and John Sweeney[1]

[1]University of Cincinnati, [2]West China Hospital, Sichuan University, [3]University of Cincinnati College of Medicine

Background: Manic youth undergo several unsuccessful medication trials prior to achieving mood stabilization. Understanding the neural effects of interventions in these youth will clarify the impact of anti-manic treatments on the neurodevelopment of bipolar disorder and may lead to identifying neurobiological response markers.
Methods: First-episode youth (FE, n=103) were randomized to blinded quetiapine (QUET) vs. lithium (Li). High-resolution MR images and fMRI during a sustained attention task were acquired from FE and healthy comparisons (HC, n=62) at baseline and Week 6. Cluster analysis and block design comparisons were performed.
Results: Response rate was greater in QUET (71%) than Li (46%, $p < 0.007$). Analysis from 68 cortical regions identified two subgroups. Group 1 with increased cortical thickness in fronto-temporo-parietal regions, consisted of 8 QUET and 8 Li. Group 2 consisted of 19 QUET and 17 Li. Group 1 (100%) had a greater response to QUET than Group 2 (52.6%, $p<0.02$). From baseline to Week 6, Li (n=54) exhibited increased activation in amygdala, putamen, posterior cingulate, precuneus, caudate, thalamus, and superior frontal gyrus and QUET (n=59) exhibited decreased activation in supramarginal and middle frontal gyri and increased activation in BA 10, 24, and 32. Response was associated with decreased activation in BA 40, inferior parietal lobule, supramarginal gyurs, and precuneus in Li and increased activation in anterior cingulate and BA 10 in QUET.
Conclusions: We identified two distinct patterns of gray matter abnormalities that were predictive of treatment response. We also identified differential neural effects and response predictors to lithium and quetiapine.
Supported By: MH077138, MH083924, MH080973
Keywords: Bipolar Disorder, Multimodal Neuroimaging, Treatment Predictions

60. Predicting Future Affective Lability From Neural Circuitry Function and Gray Matter in Youth at Risk for Bipolar Disorder

Michele Bertocci[1], Lindsay Hanford[1], Amelia Versace[1], Kelly Monk[1], Lisa Bonar[1], Satish Iyengar[1], Danella Hafeman[1], Genna Bebko[1], Cecile Ladouceur[1], Rasim Somer Diler[2], Boris Birmaher[1], and Mary Phillips[1]

[1]University of Pittsburgh, [2]University of Pittsburgh Medical Center

Background: Biomarkers of bipolar disorder are needed; identifying neural markers of known prodromal behaviors is a step toward that goal. Factors within affective lability scales are recognized as prodromal to the development of bipolar disorder. We identified neural and behavioral markers of future affective lability in at-risk youth from the Pittsburgh bipolar offspring study (BIOS) and validated these in an independent sample from the Longitudinal assessment of manic symptoms (LAMS) study.
Methods: Factors of mania/mixed, irritability, and anxiety/depression derived from affective lability scales 29-months' post fMRI scanning in 41 youth aged 14.0(sd=2.30), 19 female were predicted from clinical, demographic, and neural measures (whole brain BOLD activity during reward and emotion processing and cortical thickness) using Regularized regression analyses. Linear regression analyses were then completed in LAMS youth (n=55) using the identified variables (24-months' follow-up).
Results: Depression severity, affective lability, and left ventrolateral prefrontal, bilateral parietal, and right auditory cortices thicknesses predicted the mania/mixed factor 29 months in the future (BIOS sample adjusted r2=55.3%, $p<.001$, LAMS: r2=33.5%, p=.006). The irritability factor was predicted by depression severity, depression diagnosis, bilateral parietal, right entorhinal cortical thicknesses, and emotion processing activity in right fusiform gyrus (BIOS sample adjusted r2=44.1%, $p<.001$, LAMS: r2=29.3%, p=.004). The anxiety/depression factor was predicted by depression severity (BIOS sample adjusted r2=26.8%, $p<.001$, LAMS: r2=11.8%, p=.011).

Conclusions: Distinct combinations of clinical and neural markers predict affective lability factors in the future in two independent samples of at-risk youth suggesting the utility of these variables as objective markers of future risk and potential targets for intervention
Supported By: R01MH060952 2R01 MH73953-06A1 2R01 MH73816-06A1 2R01 MH73967-06A1 2R01 MH73801-06A1
Keywords: Outcome Prediction, Bipolar Disorder, At-Risk Youth, Cortical Thickness, BOLD fMRI

SYMPOSIUM
Mitochondrial Stress and Psychiatric Disorders
3:00 p.m. - 5:00 p.m.
Chair: Josine Verhoeven
Co-Chair: Daniel Lindqvist

61. Developing Sensitive Measurements of Mitochondrial Responses to Acute and Chronic Stress

Martin Picard[1], Caroline Trumpff[1], Anna Marsland[2], Aric Prather[3], Brett Kauffman[2], Eli Puterman[4], Kirstin Aschbacher[3], Gabriel Sturm[1], James Martin[2], Judith Caroll[5], Bruce McEwen[6], Yan Burelle[7], and Elissa Epel[3]

[1]Columbia University Medical Center, [2]University of Pittsburgh, [3]University of California, San Francisco, [4]University of British Columbia, [5]University of California, Los Angeles, [6]The Rockefeller University, [7]University of Ottawa

Background: Mitochondria are complex organelles with the own genome that generate the energy required for life and produce signals that enable stress adaptation. A systematic review of animal studies suggest that acute and chronic psychological stress can damage and impair specific aspects of mitochondrial function and health. However, evaluating this possibility in humans has been difficult due to the lack of scalable measures that accurately reflect mitochondrial health.
Methods: In one study of caregivers experiencing chronic life stress, we developed an index of mitochondrial health (MHI) by measuring and integrating the activity of three mitochondrial enzymes and mtDNA copy number from frozen leukocytes. In another study where participants were exposed to acute socioevaluative stress on two separate visits, we measured pre- and post-stress circulating cell-free levels of the mitochondrial and nuclear genomes, putative signals of intracellular stress.
Results: The MHI was sensitive to previous day mood and showed superior effect size ($n=85$, $d=0.63$, $p<0.01$) comparing groups, compared to individual enzymatic and molecular measures (all $d=0.11$-0.36, n.s.). In healthy men and women, acute psychological stress triggered robust increases in circulating cell-free mtDNA (ccf-mtDNA, $n=36$, $n2=0.57$, $p<0.0001$), but not circulating nuclear DNA.
Conclusions: We describe a new integrative index of mitochondrial health that can be applied to frozen blood leukocytes, and an approach to quantify the selective release of ccf-mtDNA. Building from these examples, this presentation will also review and discuss currently available methodologies to assess mitochondrial health and mitochondrial allostatic load (MAL) in human samples.
Supported By: NIA, NIGMS, Wharton fund
Keywords: Mitochondria, Chronic Stress, Mood, Laboratory Measurements, Systematic Review

62. Circulating Cell-Free Mitochondrial DNA – a Novel Marker of Mitochondrial Stress Associated With Suicidality and Major Depressive Disorder

Daniel Lindqvist[1], Owen Wolkowitz[2], Martin Picard[3], Lars Ohlsson[4], Francesco Saverio Bersani[5], Johan Fernström[6], Åsa Westrin[6], Christina Hough[2], Jue Lin[2], Cécile Grudet[6], Lennart Ljunggren[4], Lil Träskman-Bendz[6], Victor Reus[2], Elissa Epel[2], and Synthia H. Mellon[2]

[1]Lund University/UCSF, [2]University of California, San Francisco, [3]Columbia University, [4]Malmö University, [5]Sapienza University of Rome, [6]Lund University

Background: Mitochondrial DNA copy number (mtDNA-cn), which represents the number of mitochondrial genomes per cell, can be quantified in peripheral blood mononuclear cells (PBMC) and is thought to reflect variations in mitochondrial biogenesis. Additionally, mtDNA may be released at low levels into the circulation from mitochondria under cellular stress, resulting in circulating cell-free mtDNA (ccf-mtDNA) detectable in plasma. The source or physiological significance of ccf-mtDNA in psychiatric illness is unknown but may reflect cell damage, cell death, or bioenergetic compromise.
Methods: We enrolled suicide attempters (across diagnoses), non-suicidal subjects with Major Depressive Disorder (MDD), and healthy controls (all medication-free) in two independent cohorts ($n=110$ & $n=74$). MtDNA was quantified in cell-free plasma and in PBMCs.
Results: Ccf-mtDNA was elevated in suicide attempters and in non-suicidal MDD subjects, compared to healthy controls. These group effects were very large (Cohen's d ranging from 0.9 to 4.0, all $p<0.00001$). Ccf-mtDNA and cellular PBMC mtDNA-cn were not significantly correlated with each other ($r=0.02$, $p=0.87$), suggesting they reflect different processes. Ccf-mtDNA correlated with post-dexamethasone cortisol ($r=0.5$, $p<0.001$), suggesting that HPA-axis hyperactivity may be associated with cellular damage and release of ccf-mtDNA into the blood. Ccf-mtDNA also directly correlated with the antioxidant enzyme glutathione peroxidase ($r=0.32$, $p=0.001$), possibly reflecting a compensatory attempt to upregulate antioxidant defence mechanisms due to cellular stress.
Conclusions: Ccf-mtDNA may represent a novel marker of cellular stress, which is increased in certain psychiatric conditions. These results call for replication in larger cohorts and in longitudinal studies.
Supported By: This study was funded by grants from the National Institute of Mental Health (NIMH) (Grant Number R01-MH083784), the O'Shaughnessy Foundation, the Tinberg family, and grants from the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC), and the Bernard and Barbro Foundation. This project was also

supported by National Institutes of Health/National Center for Research Resources (NIH/NCRR) and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Daniel Lindqvist was supported by the Swedish Research Council (registration number 2015-00387), Marie Sklodowska Curie Actions, Cofund (Project INCA 600398), the Swedish Society of Medicine, the Söderström-Königska Foundation, the Sjöbring Foundation, OM Persson Foundation and the province of Scania (Sweden) state grants (ALF). The Blackburn lab is supported in part by gifts from the Shaklee Corporation and the Mars, Incorporated.
Keywords: mtDNA Copy Number, Major Depressive Disorder (MDD), Suicide Attempts, Circulating Cell-Free DNA, Antioxidant Enzymes

63. Socioeconomic Disadvantage and Whole Blood Mitochondrial DNA Copy Number Decline Over 10-Years: The Coronary Artery Risk Development in Young Adults (CARDIA) Cohort

Robert-Paul Juster[1], Nancy Adler[2], Martin Picard[3], Elissa Epel[2], Barbara Sternfield[4], Karen Matthews[5], David Jacobs[6], and Eli Puterman[7]

[1]Columbia University & New York State Psychiatric Institute, [2]University of California, San Francisco, [3]Columbia University, [4]Kaiser Permanente Northern California, [5]University of Pittsburgh, [6]University of Minnesota, [7]University of British Columbia

Background: Low socioeconomic status (SES) predicts poor health throughout life. One's subjective social status (SSS) can be an even stronger predictor of health than SES. We assessed SES and SSS in relation to 10-year changes in whole-blood mitochondrial DNA copy number (mtDNAcn), an emerging cellular aging biomarker.
Methods: Years 15 and 25 CARDIA data for 992 black and white men and women aged 33-47 were analyzed. SSS was assessed using the MacArthur Ladder Scale representing self-ranked standing (1-9 scale) within the community. mtDNAcn was measured by quantitative PCR. We employed linear mixed modeling to estimate baseline (Y15) and 10-year mtDNAcn rate of change (Y15 to Y25) as a function of either education, income, or SSS at Y15 in three independent analyses while adjusting for the other two variables and age, sex, race/ethnicity, physical activity, and BMI.
Results: SES did not predict baseline or changes in mtDNAcn. By contrast, higher SSS was significantly associated with lower baseline (b=-7.76, 95%CI=-13.06, -2.47) and a slower rate of decline over 10-years (SSS*time interaction: b=6.27, 95%CI=0.65, 11.89). Follow-up analysis revealed that the estimated rate of decline in mtDNAcn over 10-years was -47.58 (95%CI=-60.10, -35.06) for those 1SD above the SSS mean and -67.49 (95%CI=-79.99, -54.99) below the SSS mean.
Conclusions: Greater SSS was associated with lower mtDNAcn at baseline and also delayed DNA loss over 10-years. Irrespective of objective SES, it is possible that higher subjective social standing contributes to stress-related mitochondrial cellular aging in early adulthood but is not associated with long-term declines.
Supported By: The CARDIA study is supported by contracts HHSN268201300025C, HHSN2682 01300026C, HHSN268201300027C, HHSN268201300028C, HHSN26820 1300029C and HHSN268200900041C from the National Heart, Lung, and Blood Institute (NHLBI), the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005). Cell aging assays were supported by the John & Catherine MacArthur Foundation Research Network on Socioeconomic Status and Health and by the National Heart, Lung and Blood Institute of the National Institutes of Health under award number K99/R00 HL 109247. Robert-Paul Juster is funded by the Canadian Institutes of Health Research Banting Postdoctoral Award.
Keywords: Mitochondria, Socioeconomic Status, Psychosocial Stress, Depressive Symptoms

64. Early Stress and Mitochondrial DNA in Human and Mouse Models

Audrey Tyrka[1], Kathryn Ridout[2], Stephanie Parade[3], Mizan Gaillard[2], Ronald Seifer[4], Hung-Teh Kao[2], Barbara Porton[2], Lawrence Price[1], and Kevin Bath[2]

[1]Butler Hospital - Brown Medical School, [2]Brown University, [3]Bradley Hospital - Brown Medical School, [4]Bradley Hospital - Brown University

Background: Recent studies have implicated mitochondria in the effect of early trauma on risk for psychiatric disorders. Here we present results of a study of preschool-aged maltreated children and a study of a mouse model of early life stress (ELS).
Methods: Study 1: Children aged 3-5 were identified through the local child welfare agency (n=133, maltreated) or preschools and pediatric clinics (n=117, control). Home visits at baseline and 6-month follow-up included assessments of stressors and symptoms, and saliva collection for DNA and qPCR measurement of mitochondrial DNA copy number (mtDNAcn).

Study 2: C57BL/6N male mice were unhandled (UHC) or reared with restricted bedding materials from p4-p11 (ELS). Hippocampal samples across development (N=5/cell) from ≥2 different litters were isolated and cDNA synthesized. Mitochondrial oxidative genes (NADH:ubiquinone oxidoreductase subunits 1-6; cytochrome b; cytochrome c oxidase I-III; ATP synthase 6 and 8) were run in multiplex with 18S as standard.
Results: Study 1: Maltreatment was associated with higher mtDNAcn ($p<.05$). Baseline mtDNAcn was positively associated with baseline internalizing behaviors ($p<.05$), and follow-up mtDNAcn was associated with baseline and follow-up internalizing ($p's<.005, <.0001$).

Study 2: Gene expression increased with development ($p's<.0001$). ELS significantly reduced expression of a number of mitochondrial genes ($p's<.05$), particularly at p28 and p50.
Conclusions: This is the first evidence of altered mtDNAcn with stress in children; results are consistent with data from

adults with a history of childhood adversity. ELS reduced mtDNA gene expression in mouse hippocampus during development. Altered mitochondrial function may influence mitochondrial biogenesis and the pathogenesis of stress-related psychiatric conditions.
Supported By: Brown BIBS/NPNI New Frontiers Award (ART, KB); R01 MH083704 (ART)
Keywords: Mitochondria, Mitochondrial Biogenesis, Early Life Stress, Child Maltreatment, Developmental Psychopathology

SYMPOSIUM
Novel Molecular Targets for Next Generation Experimental Therapeutics in Mood Disorders: From Animal Models to Clinical Trials

3:00 p.m. - 5:00 p.m.
Chair: James Murrough
Co-Chair: Manish Jha

65. From Stress Resilience to Novel Therapeutics: KCNQ Channel Openers and Other Approaches Emerging From Translational Neuroscience

James Murrough[1], Aaron Tan[1], Laurel Morris[1], Sara Costi[1], Nicholas Van Dam[2], Emily Stern[1], Eric Nestler[1], and Ming-Hu Han[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Melbourne School of Psychological Sciences

Background: Up-regulation of neuronal KCNQ channels within the ventral tegmental area (VTA)—nucleus accumbens (NAc) reward pathway has emerged as an essential mechanism of stress resilience, and KCNQ channel openers show antidepressant activity in rodent models. Base on this work, we have conducted a proof-of-concept (POC) clinical trial of the KCNQ channel opener ezogabine in patients with major depressive disorder (MDD) with concurrent measurement of neurocircuit function using functional MRI (fMRI).
Methods: Eighteen subjects with MDD were enrolled in an open-label POC study of ezogabine titrated to 900mg daily with resting state fMRI collected at baseline and end of treatment (week 10). The primary clinical outcome was depression severity measured using the Montgomery Åsberg Depression Rating Scale (MADRS). Resting state functional connectivity (RSFC) of two striatal seeds selected from the Harvard-Oxford 470 atlas was computed in order to interrogate the human homologue of the reward circuit implicated in animal models [NAc, ventral caudate (VC)].
Results: MADRS score significantly decreased at study end [-13.7 ± 9.6, $t(17)=6.01$, $p<0.001$]. There was no effect of time on RSFC. There was a significant interaction between time and MADRS score: greater improvement in depression was associated with reduced RSFC between the VC and the anterior mid-cingulate (whole-brain cluster corrected $p<0.05$, with AFNI's updated autocorrelation function).
Conclusions: These data provide initial support for the hypothesis that KCNQ channel openers may represent a mechanistically novel class of antidepressants. These agents may work via a neurocircuit that involves the ventral caudate and anterior mid-cingulate. Testing in larger, randomized controlled trials is required.
Keywords: Depression, Antidepressant, Resilience

66. Neuroimaging Evidence for Targeting Abnormal Responses to the Social Environment in Major Depressive Disorder

David Hsu[1], Ashley Yttredahl[1], and Anjali Sankar[1]

[1]Stony Brook University

Background: Responses to social life events is a critical factor in the prognosis of major depressive disorder (MDD). Using functional magnetic resonance imaging (fMRI), we examined neural responses to social rejection and acceptance. In a pilot study, we manipulated behavioral responses to rejection by using transcranial direct current stimulation (tDCS). These studies will help to identify novel targets for next generation therapeutics focused on adaptive social functioning in MDD.
Methods: Twenty women with current MDD and 20 matched healthy controls (HC) (mean age=30 years) performed an online dating task in which they were rejected or accepted by others during fMRI. In the pilot study, 13 HC men and women (mean age=21 years) were given acute tDCS or sham stimulation over the right ventrolateral prefrontal cortex (vlPFC), an area involved in emotion regulation, followed by social rejection.
Results: MDD subjects showed behavioral and neural hyperresponsivity to rejection, including strong activation in the right anterior insula ($P_{FWE\text{-}whole\text{-}brain} < 0.001$), which spread anteriorly into the right vlPFC. Weaker activation was found in HCs. Both groups reported feeling "happy and accepted" after acceptance. In HC but not MDD subjects, this response was associated with activity in the left and right nucleus accumbens ($P's < 0.001$). TDCS attenuated changes in affect, self-esteem and rumination following rejection, although only trends were observed in this preliminary sample.
Conclusions: Our findings highlight abnormal responses to the social environment in MDD. Targeting these pathways may be effective in MDD with a rejecting life event, and/or those with high rejection sensitivity.
Supported By: K01 MH085035; Department of Psychiatry Pilot Grant, Stony Brook Medicine
Keywords: Social Rejection, tDCS, Major Depressive Disorder (MDD), Insula, Accumbens

67. Brain Th17 Cells in Mice With Depressive-Like Behavior: Towards Novel Treatment Targets

Eleonore Beurel[1]

[1]Univeristy of Miami

Background: Depression is prevalent and debilitating and has been linked to inflammation. Inflammation increases CD4 cells that produce IL-17A (Th17 cells) that promote depression in mice. We examined the mechanisms by which Th17 cells promote depressive-like behaviors.

Methods: T cell subtypes were transferred into recipient mice and effects on the learned helplessness model of depression were determined. Characteristics of Th17 cells in mouse hippocampus were determined by flow cytometry.
Results: Th17 cells, but not Th1 cells, promoted depressive-like behaviors, and accumulated in prefrontal cortex and hippocampus but not in cerebellum, of mice exhibiting stress-induced depressive-like behavior (n=4-13, p=0.001). Adoptive transfer of Th17 cells into Rag2-/- mice, which are devoid of endogenous T cells, was sufficient to induce depressive-like behavior, demonstrating that increased peripheral Th17 cells can affect behavior (n=5-9;p=0.022). Moreover, adoptively transferred Th17 cells accumulated in the hippocampus of learned helpless mice, and induced endogenous Th17 cell differentiation (n=4-12;p=0.001;p<0.0001). Characterization of hippocampal Th17 cells in learned helpless mice revealed that the Th17 cells express CCR6 and IL-23R (n=8-17;p=0.003;p=0.0014), which have previously been shown to be markers of pathogenic Th17 cells, and CXCR5, a marker of follicular T cells (n=8-19;p=0.0002). CCR6, but not CXCR5, was required to promote Th17 cell-dependent depressive-like behavior (n=11;p=0.0456). PD-1 expression on Th17 cells was increased in the mice that received CCR6 deficient Th17 cells (n=9;p=0.05), providing a possible link between T follicular cells expressing PD-1 and pathogenic CCR6 expressing Th17 cells in the brain.
Conclusions: Th17 cells and associated pathways are novel molecular targets for depression.
Supported By: MH104656, MH110415
Keywords: Depression, Inflammation, Hippocampus

68. Blood Brain Barrier Dysfunction Selectively Predicts Poorer Outcomes With SSRI Monotherapy vs. Antidepressant Combinations: Clinical Utility of Novel Astrocytic Marker

Manish Jha[1], Abu Minhajuddin[2], Bharathi Gadad[2], and Madhukar Trivedi[2]

[1]UT Southwestern, [2]The University of Texas Southwestern Medical Center

Background: Elevated S100 calcium binding protein B (S100B) levels in depressed patients may reflect greater blood brain barrier (BBB) dysfunction, which in turn can facilitate neuroinflammation and impair dopamine neurotransmission. This study tested the hypothesis that higher S100b levels predict poorer outcomes with selective serotonin reuptake inhibitor (SSRI) medications as compared to combination containing dopaminergic antidepressant.
Methods: S100B was measured at baseline with enzyme-linked immunosorbent assay in Combining Medications to Enhance Depression Outcomes participants (n=153). Treatment arms included bupropion-plus-escitalopram, escitalopram-plus-placebo, and venlafaxine-plus-mirtazapine. Depression severity was measured with 16-item Quick Inventory of Depressive Symptomatology Self-Report and anhedonia was measured with 3 items of 30-item Inventory of Depressive Symptomatology. Differential changes in depression severity and anhedonia over acute-phase (baseline to week 12) in the three treatment arms were tested with logS100B-by-treatment-arm interaction in mixed model analyses after controlling for age, gender and body mass index.
Results: There was a significant logS100B-by-treatment-arm interaction for anhedonia (F=3.21; df=2, 142; p=0.04) but not for overall depression severity (F=1.99; df=2, 142; p=0.14). Higher logS100B levels were associated with smaller reductions in anhedonia (effect size=0.67, p=0.047) in escitalopram monotherapy but not the other two arms. Correlation coefficients of anhedonia severity averaged over acute-phase (including baseline) with baseline S100B levels were 0.57, -0.19, and 0.22 for escitalopram monotherapy, bupropion-plus-escitalopram and venlafaxine-plus-mirtazapine arms.
Conclusions: High baseline S100B levels in depressed patients resulted in poorer response to escitalopram monotherapy. Addition of bupropion, a dopaminergic antidepressant, partially mitigated this effect. S100B is a promising target to identify novel therapeutics to reduce anhedonia in depressed patients.
Supported By: N01 MH-90003; The Hersh Foundation; and The Jordan Harris Foundation
Keywords: S100B, Inflammation, Blood Brain Barrier, Anhedonia, Predictive Biomarkers

SYMPOSIUM
Using Translational Neuroscience to Accelerate the Development of CNS Therapeutics

3:00 p.m. - 5:00 p.m.
Chair: Gregory Light
Co-Chair: Mitsuyuki Matsumoto

69. The Postmortem Human Brain to Characterize Novel Drug Targets for Psychiatric Disorders: Using FKBP5 as an Example

Natalie Matosin[1], Silvia Martinelli[1], Cristiana Cruceanu[1], Gustavo Turecki[2], and Elisabeth Binder[1]

[1]Max-Planck Institute of Psychiatry, [2]McGill University

Background: Disruptions to the levels or functions of molecules in psychopathology form the rationale for their use as drug targets. However, changes in target molecules and their bioavailability can influence drug efficiency in patients. Characterizing alterations of key molecules directly in the brain can help develop appropriate pharmacological strategies. FKBP5 is a novel cross-disorder drug target for psychiatric conditions. In-depth characterization of brain-expressed FKBP5 is required to transition FKBP5-targeting drugs into the clinic.
Methods: RNA sequencing was performed in postmortem samples from the anterior cingulate cortex (ACC) and hippocampus (HIP) of 13 bipolar disorder (BPD) and 13 controls with the Illumina HiSeq2000 platform. Reads were aligned and gene/isoform-level counts were derived. Immunohistochemistry analysis (IHC) of FKBP5 expression was also performed.
Results: A truncated transcript of FKBP5 (variant 4) was increased in BPD vs controls (ACC -66.39%; HIP +35.76%). In the ACC, variant 1 was also increased in BPD (+70.33%), while

variant 2 was decreased (-36.81%). These alterations were not seen in HIP. IHC indicated that total FKBP5 expression might be limited to neurons, with co-localized staining of FKBP5 with neuronal marker NeuN, but not GFAP.
Conclusions: These data indicate that FKBP5 is altered in BPD in a transcript-specific manner. Notably a variant 4, encoding a truncated FKBP5 protein, was increased in BPD in both the ACC and HIP. This truncated FKBP5 protein likely has unique functionality, thus alterations in this protein might have implications for therapeutic efforts targeted at FKBP5. Further analyses are now being conducted to determine the functional significance of variant 4.
Supported By: NHMRC; Alexander von Humboldt Stiftung; International Brain Research Organisation.
Keywords: FKBP5, Human Postmortem Brain, Novel Treatments, Stress, Bipolar Disorder

70. Toward Understanding a Mouse Model of Schizophrenia: From Cellular and Behavioral Phenotypes to a Biomarker of Pathophysiology

Megumi Adachi[1]

[1]Astellas Research Institute of America LLC

Background: Animal models of schizophrenia that present not only pathophysiology but also a wide array of symptoms affected in the patients are in an urgent need. Mounting evidence from human genetics studies indicate an involvement of gene networks related to NMDA receptor/CaMKIIa signaling. Recently, we generated a mouse line constitutively lacking CaMKIIa gene and reported a cellular feature, immature dentate gyrus (iDG), characterized by increased number of immature neuronal progenitors and a concomitant decrease in mature neurons in hippocampus. More importantly, iDG was detected in postmortem brains of a subset of schizophrenia and bipolar, raising a possibility that this cellular phenotype may present underlying pathophysiology of schizophrenia.
Methods: Using CaMKIIa-hKO mice, we conducted a broad array of behavioral tests relevant to symptoms in schizophrenia. In an attempt to identify a biomarker specific to a behavioral deficit, electroencephalogram (EEG) recording was also carried out.
Results: CaMKIIa-hKO mice were hypoactive in home cage environment and presented less anxiety-like behavior. Furthermore, strong deficits in short and long-term memory formation were detected. Based on the cognitive impairment as well as iDG observed in CaMKIIa-hKO mice, we recorded EEG from an electrode implanted in hippocampus. CaMKIIa-hKO mice showed an increase in auditory-evoked high-frequency gamma power although baseline gamma was unchanged. Additionally, some of measures in event-related potentials were altered.
Conclusions: Collectively, CaMKIIa-hKO mice displayed some of the behavioral and cellular features reminiscent to schizophrenia. EEG measures suggest this mouse line potentially provide a unique opportunity to lay out a therapeutic strategy.
Supported By: N/A
Keywords: Schizophrenia, Mouse Model, EEG, Hippocampus, CaMKII

71. Convergence of Glutamatergic Mechanisms for the Generation of High Frequency EEG Noise

Steven Siegel[1] and Robert Featherstone[1]

[1]University of Southern California

Background: The negative symptoms remain among the most disabling and treatment refractory issues for people with schizophrenia Gap: Animal models of the negative symptoms of schizophrenia have been particularly challenging due to a dearth of manipulations with face or construct validity. Additionally, the lack of effective treatments for social and motivational deficits has impaired the ability to assess positive predictive validity from preclinical to clinical application. Despite these limitations, several lines of investigation suggest that alterations of N-Methyl D-Aspartate receptor-mediated glutamate transmission is related to negative symptoms.
Methods: Therefore, we will present data from three animal models of disrupted NMDAR-mediated glutamate signaling that display alterations in social interactions and other measures of self-care. These include reduction of NMDAR1 in either pyramidal cells or Parvalbumin-positive interneurons, as well as mice with reduction of Src-kinase, which is a downstream mediator of NMDAR function. Additionally, we evaluate the association between high frequency resting state electroencephalographic activity and social function in these model systems.
Results: Data indicate that mice with altered NMDAR1 in either pyramidal cells or PV-interneurons, as well as those with reduced Src display statistically significant ($P<0.05$) impairments in social interactions and related behaviors. Additionally, social interactions are inversely associated with high frequency EEG, and pharmacological remediation of EEG was predictive of behavioral improvements.
Conclusions: We propose that high frequency EEG activity at rest is a physiological biomarker of negative symptoms and may represent a clinical endpoint in early phase clinical trials of medications to treat negative symptoms.
Supported By: R01 MH075916-05
Keywords: EEG, Schizophrenia, Mouse, Translational Research, Biomarkers

72. One Pill Can Enhance Auditory Information Processing and Learning in Schizophrenia Patients: Should We Rethink the Way We're Approaching Therapeutic Development for Schizophrenia?

Neal Swerdlow[1], Savita Bhakta[1], Jo Talledo[1], Daniel Franz[1], Brinda Rana[1], and Gregory Light[1]

[1]University of California San Diego

Background: Early auditory information processing (EAIP) is a root cause of impairment in schizophrenia; interventions that enhance EAIP in schizophrenia patients are thus rational

therapeutic targets. Our studies assess acute drug effects on EAIP as potential biomarkers for therapeutic sensitivity.
Methods: Acute drug effects on EAIP and learning in a "sound sweeps" frequency modulation task (FMT) component of an effective targeted cognitive training (TCT) suite were tested in healthy subjects (HS; n≈90) and antipsychotic -medicated schizophrenia patients (n≈80). EAIP measures include prepulse inhibition (PPI), auditory steady state response (ASSR) and mismatch negativity (MMN).
Results: The NMDA antagonist, memantine (20 mg) significantly enhanced PPI, MMN and ASSR (p's<0.04-0.0015). The psychostimulant, amphetamine (10 mg) enhanced learning (post- vs. pre-training) in the FMT (p<0.002), and this learning was sustained for at least 1 week. Amphetamine normalized PPI (60 ms interval) in this cohort of schizophrenia patients. Moderating effects of specific SNPs were detected on some drug effects on EAIP measures.
Conclusions: Procognitive development for schizophrenia has focused on drugs added daily to antipsychotics regimens, to correct a hypothesized biological deficit, without considering the ability of that drug to meet specific demands of a cognitive intervention. We suggest "rethinking" this model, to focus on biomarker-sensitive interventions that augment neural processes engaged by cognitive therapies. Because positive drug effects on EAIP are evident after a single pill, one "paradigm shift" in treatment models would pair an acute drug challenge with a session of a cognitive intervention (e.g. TCT), thereby constraining the amount, timing and setting of medication use.
Supported By: MH59803, MH094320, NARSAD Distinguished Investigator Award
Keywords: Amphetamine, Memantine, Schizophrenia, Prepulse Inhibition, Mismatch Negativity

SYMPOSIUM
Convergence Between Human and Animal Research on Risk Factors for Substance Use Initiation and Continuation

3:00 p.m. - 5:00 p.m.
Chair: Hugh Garavan

73. Multi-Modal Predictors of Cannabis Use Initiation in Adolescents

Hugh Garavan[1] and Phil Spechler[1]

[1]University of Vermont

Background: Cannabis use during adolescence might precipitate negative consequences for brain function and health. Thus, predicting adolescent cannabis use prior to any exposure could guide proactive interventions and inform the etiology of substance abuse by disentangling predictors from consequences of use.
Methods: Data were from the IMAGEN longitudinal study of adolescence. All participants (n=1,581) were cannabis-naïve at age 14. Those reporting any cannabis use by age 16 were included in the outcome group (N=365, males n=207). Cannabis-naïve participants at 14 and 16 were the comparison group (N=1,216, males n=538). Psychosocial, brain, and genetic features were measured at age 14 prior to any exposure. Cross-validated regularized logistic regressions for each sex performed feature selection and obtained prediction error statistics (ROC AUC) on independent observations.
Results: Models reliably predicted use (Males: range ROC AUC across use levels=[0.65-0.74]; Females: range ROC AUC =[0.74-0.82]) and contained psychosocial features (personality factors such as novelty seeking and disorderliness; alcohol and nicotine use; parental cannabis use) common to both sexes. However, males and females exhibited distinct brain predictors (regional GMV and activations associated with inhibitory control and face processing) that failed to predict use in the opposite sex or predict binge drinking in independent samples of same-sex participants. Collapsed across sex, genetic variation on catecholamine and opioid receptors also predicted use (range ROC AUC= [0.54-0.60]).
Conclusions: By leveraging machine learning techniques applied to a large multimodal dataset, we report that the initiation of cannabis use during adolescence is predicted for each sex with a risk profile containing psychosocial and sex-specific brain features.
Supported By: NIGMS P20GM103644; the European Union-funded FP6 Integrated Project
Keywords: Cannabis, Adolescence, MRI, Prediction

74. The Role of Poor Response Inhibition in Onset and Growth of Substance Use and Aggressive Behaviours

Patricia Conrod[1]

[1]University of Montreal

Background: The ability to inhibit pre-potent and goal inappropriate responses (i.e., response inhibition) is a key executive function for self-regulation of behaviours. It is also identified as a precursor to substance misuse and aggression in adolescents. However, it remains to be explained how the simple process of stopping a behavioural response, is implicated in emergence of substance use disorders and proactive interpersonal aggression.
Methods: The Co-Venture study followed 3800 Grade 7 youths assessed annually from school for 5 years on self-reported alcohol and drug use and misuse, cognitive functioning (episodic memory, working memory, perceptual reasoning, response inhibition and reward learning) and self-reported mental health symptoms (see O'Leary-Barrett et al., 2017). Two-part latent growth models with lagged and time-varying covariates investigated the relationship between response inhibition and substance use and aggression from a developmental perspective.
Results: Models indicated that poor response inhibition during childhood was associated with the tendency to be an early substance onset user and to be victimized by peers. These outcomes were in turn related to further decreases in response inhibition and the tendency to develop hostile attributional styles, which respectively predicted growth in substance misuse and perpetration of interpersonal aggressive acts.

Conclusions: The findings suggest a causal pathway from poor response inhibition during childhood to more severe substance use and aggressive behaviours in late adolescence and suggest the need for targeted interventions that are designed to help adolescents improve response inhibition and cognitive control.
Supported By: Canadian Institutes of Health Research
Keywords: Response-Inhibition, Aggression, Substance Abuse, Adolescence

75. Risky Decision Making in Rats is Associated With Markers of Addiction Vulnerability

Catharine Winstanley[1]

[1]University of British Columbia

Background: Although risky decision making is associated with substance dependence, it is difficult to ascertain from clinical data whether this cognitive impairment is a cause or consequence of drug use. Animal models can play a critical role in this regard, and permit investigation into the neurobiological mechanisms regulating maladaptive choice.
Methods: We trained male Long-Evans rats (n: 90) on the rat Gambling Task (rGT), loosely based on the Iowa Gambling Task, to determine whether choice preference influenced, and was influenced by, cocaine self-administration. We then bred TH:Cre rats (male; n: 32), which express cre recombinase in neurons capable of synthesizing tyrosine hydroxylase, and infused an adeno-associated virus that induces expression of the inhibitory DREADD under the control of a cre-promoter into the nucleus accumbens. These rats were then trained on the rGT, and the DREADD ligand clozapine-n-oxide (CNO) administered.
Results: Cocaine self-administration exacerbated risky choice in risk-preferring rats ($F_{6,31} = 3.24$, $p = 0.01$). This decision-making deficit correlated with greater cue-induced incubation of craving ($r = 0.61$, $p = 0.03$). In contrast, the choice patterns of optimal decision-makers were unaffected by drug-taking. The addition of reward-concurrent cues that increased in complexity with the size of the win significantly increased risky choice and potentiated the ability of cocaine self-administration to bias preference towards risky outcomes. CNO decreased risky choice selectively in transgene positive rats ($F_{9,81} = 2.074$, $p = 0.04$).
Conclusions: These data demonstrate that poor decision making prior to contact with addictive drugs is associated with a pro-addictive behavioral phenotype which may be driven by hypersensitivity to dopamine release in the accumbens.
Supported By: CIHR
Keywords: Dopamine, Rat Gambling Task, Cocaine, DREADDs

76. Dynamic Changes in Risky Decision-Making Predict Imminent Heroin Use in Opioid Users Studied Longitudinally Through the First Months of Treatment

Anna Konova[1], Silvia Lopez-Guzman[1], Adelya Urmanche[1], Stephen Ross[2], Kenway Louie[1], John Rotrosen[2], and Paul Glimcher[1]

[1]New York University, [2]New York University School of Medicine

Background: Opioid overdose is now the leading cause of accidental death in the U.S. Opioid use during treatment increases overdose risk; thus, identifying predictors of opioid use in treatment-seekers at a timescale amenable to intervention is a priority. Here we tested the hypothesis that the value of risky prospects is enhanced when individuals are most vulnerable to use heroin.
Methods: 79 treatment-seekers completed 1-15 sessions over 7 months (mean/subject=6, SD=3.9). At each session, subjects made decisions about risks and rewards, and we objectively monitored heroin use. We modeled subjects' decisions as two parameters: risk tolerance and ambiguity tolerance, capturing behavior involving known and unknown risk, respectively. This allowed us to predict heroin use from session-to-session change in the parameters via time-lagged mixed-effects logistic regression. 12 subjects (study ongoing) additionally completed the same procedures during multi-band fMRI.
Results: Of 605 total sessions, 288 (47%) were heroin positive. Only an increase in ambiguity tolerance was predictive of prospective heroin use at the timescale examined [$t(577) = 3.39$, $P < 0.001$], supporting our hypothesis that the value of the (more) risky prospects is enhanced when individuals are most vulnerable. The fMRI data revealed activity in the striatum and VMPFC encoded the value of the ambiguous prospects. This in turn correlated with striatum-VMPFC connectivity at rest, together suggesting coordinated activity in the brain's valuation system might underlie both the observed behavior change and heroin use vulnerability.
Conclusions: Treatment-monitoring and -intervention efforts targeting decision-making (and thus the valuation system) may help reduce incidence of relapse in a population at risk for overdose death.
Supported By: F32DA039648; R01DA043676
Keywords: Computational Psychiatry, Opioid Addiction, Risky Decision-Making, Relapse and Treatment Outcome, Brain Imaging, fMRI

SYMPOSIUM
Using Neuroimaging to Generate Predictive Models for Dimensional Psychiatry
3:00 p.m. - 5:00 p.m.
Chair: Dustin Scheinost

77. Intrinsic Brain Architecture Predicts Future Attentional and Mood Problems in a Normative Pediatric Sample

Susan Whitfield-Gabrieli[1], Stephen Bailey[2], Laurie Cutting[2], and Silvia Bunge[3]

[1]MIT, [2]Vanderbilt, [3]Berkeley

Background: Previously we and others have discovered ways in which neuroimaging could be used to identify brain network

pathologies in children who are at familial risk for psychiatric disorders but who are not currently diagnosed with any disorder. Here, we expand on the previous findings by investigating longitudinally a normative sample of children.

Methods: We tested whether resting state fMRI, can predict individual children's developmental trajectories towards attentional problems characteristic of Attention Deficit Hyperactivity Disorder (ADHD), or internalizing problems characteristic of major depression (MDD). We analyzed neuroimaging and behavioral data from a longitudinal study of children assessed at age 7 (N=94), and again at age 11 (N=54). We tested whether specific connectivity patterns would predict scores on the Child Behavior Checklist (CBCL), a parental report assessment used to screen for behavioral problems and to predict psychiatric illnesses.

Results: Greater connectivity at age 7 between medial prefrontal cortex (MPFC), a core node in the default mode network (DMN), and dorsolateral prefrontal cortex (DLPFC) predicted the development of attentional problems characteristic of ADHD by age 11. Weaker connectivity between a region implicated in mood, the subgenual anterior cingulate cortex (sgACC), and DLPFC at age 7 predicted the development of internalizing behaviors by age 11.

Conclusions: These findings further our understanding of the neurobiological vulnerabilities that foster the deterioration of mental health, but also could inform early identification and preventative treatment for children who, regardless of a documented family history of mental disorders, have a neurobiological vulnerability for ADHD or MDD.

Keywords: Resting State Networks, ADHD, MDD, Prediction

78. Adolescent Impulsivity Phenotypes Characterized by Distinct Brain Networks: A 4-Year Follow up

Kathy Ruddy[1], Laura Milena Rueda Delgado[1], Tobias Banaschewski[2], Gareth Barker[3], Arun Bokde[1], Uli Bromberg[4], Christian Buchel[4], Erin Burke Quinlan[3], Sylvane Desrivières[3], Herta Flor[2], Vincent Frouin[5], Andreas Heinz[6], Penny Gowland[7], Bernd Ittermann[8], Jean-Luc Martinot[9], Marie-Laure Paillere Martinot[10], Herve Lemaitre[9], Frauke Nees[2], Dimitri Papadopoulos Orfanos[5], Tomas Paus[11], Luise Poustka[2], Sarah Hohmann[2], Juliane Frohner[12], Michael Smolka[12], Henrik Walter[6], Gunter Schumann[3], Hugh Garavan[13], and **Robert Whelan**[1]

[1]Trinity College Dublin, Ireland, [2]Heidelberg University, [3]King's College London, [4]University Medical Centre Hamburg-Eppendorf, [5]Neurospin, Commissariat à l'Energie Atomique, [6]Chrité Universitätsmedizin Berlin, [7]University of Nottingham, [8]Physikalisch-Technische Bundesanstalt (PTB), [9]INSERM U1000, [10]APHP, [11]Rotman Research Institute, [12]Technische Universität Dresden, [13]University of Vermont

Background: Impulsivity is a characteristic feature of adolescence. We previously reported in a large (n=1,896) sample of 14-year-olds that impulsivity phenotypes were differentially related to particular brain networks active during the Stop Signal Task (SST; Whelan et al., 2012). Here, we investigated how individual differences in these networks at age 14 relate to inhibitory control networks and impulsivity phenotypes at age 18.

Methods: Participants completed the SST under fMRI at both age 14 and age 18. Measures of behavioral impulsivity, substance misuse and ADHD symptoms were also obtained at both time points. A factor analysis on regions of interest was applied to fMRI data. Changes in brain networks were modelled using a linear mixed effects approach.

Results: Factor analysis with 31 brain regions of interest (ROIs) revealed remarkably similar networks at age 14 and 18. All six networks associated with failed inhibition were identical at age 14 and 18, while successful inhibition trials revealed minor changes in brain dynamics in a parietal network. Notably, individual differences in brain activity in a right prefrontal network at age 14 predicted activity in this network at age 18 ($p<10^{-10}$), as did activity in the default mode ($p<10^{-5}$) and a substantia nigra/subthalamic nucleus network ($p<.005$). Changes over the four-year period in the basal ganglia network during successful and failed inhibition were modulated by the extent of cigarette use ($p=0.011$ and $p<0.001$, respectively).

Conclusions: Individual differences in task-related brain activity at age 14 are predictive of activity at age 18 in similar networks.

Supported By: This work received support from the following sources: the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-related behaviour in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC Advanced Grant 'STRATIFY' (Brain network based stratification of reinforcement-related disorders) (695313), ERANID (Understanding the Interplay between Cultural, Biological and Subjective Factors in Drug Use Pathways) (PR-ST-0416-10004), BRIDGET (JPND: BRain Imaging, cognition Dementia and next generation GEnomics) (MR/N027558/1), the FP7 projects IMAGEMEND(602450; IMAging GEnetics for MENtal Disorders) and MATRICS (603016), the Innovative Medicine Initiative Project EU-AIMS (115300-2), the Medical Research Council Grant 'c-VEDA' (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the Swedish Research Council FORMAS, the Medical Research Council, the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, the Bundesministeriumfür Bildung und Forschung (BMBF grants 01GS08152; 01EV0711; eMED SysAlc01ZX1311A; Forschungsnetz AERIAL), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-1, SM 80/7-2, SFB 940/1). Further support was provided by grants from: ANR (project AF12-NEUR0008-01 - WM2NA, and ANR-12-SAMA-0004), the Fondation de France, the Fondation pour la Recherche Médicale, the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012; the National Institutes of Health, Science Foundation Ireland (16/ERCD/3797), U.S.A. (Axon, Testosterone and Mental Health during Adolescence; RO1 MH085772-01A1), and by NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence.

Keywords: Adolescence, Impulsivity, Substance Use, BOLD Functional MRI, Longitudinal Brain Imaging

79. Transdiagnostic Prediction of Memory and Cognitive Abilities From Functional Connectivity Data: A Multidimensional Connectome-Based Predictive Modeling Study

Dustin Scheinost[1], Siyuan Gao[2], Abigail Greene[1], and R. Todd Constable[1]

[1]Yale School of Medicine, [2]Yale University

Background: Machine learning algorithms are revealing robust individual differences in patterns of functional connectivity that predict behavioral measures. We demonstrate that multidimensional connectome-based predictive modeling (mdCPM)—where connectivity matrices, or connectomes, from seven different conditions, including resting-state, are optimally combined into a single predictive model—can predict memory and cognitive abilities across individuals with schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder (ADHD) and healthy controls.
Methods: These analyses use data from the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study. Each participant performed one resting-state and six task fMRI runs in the scanner. The sample consisted of 73 healthy controls, 34 participants with bipolar disorder, 31 participants with schizophrenia, and 31 participants with ADHD. Cognitive abilities were measured using the Letter Number Sequencing, Vocabulary, and Matrix Reasoning scales from the Wechsler Adult Intelligence Scale. Connectomes were constructed with standard methods.
Results: Models generated from the mdCPM significantly predicted memory and cognitive abilities with leave-one-out cross-validation ($p<0.01$, corrected, range $r=0.38$-0.47). All models were complex and included multiple connections within and between canonical large-scale networks (e.g., frontoparietal, default mode, salience). In an exploratory analysis, we examined all combinations of tasks to determine which combinations generated the best predictions. For all scales, all tasks were needed to generate the best performing models.
Conclusions: These results suggest that multidimensional models that combine information from several task connectomes can predict cognitive abilities in a transdiagnostic manner. This approach may be helpful in characterizing transdiagnostic brain-behavior relationships, as proposed under the research domain criteria initiative.
Supported By: unfunded
Keywords: Connectome, Prediction, Transdiagnostic, Schizophrenia, Bipolar Disorder

80. Continuous and Categorical Prediction of Cocaine Treatment Outcomes

Sarah Yip[1], Dustin Scheinost[1], Marc Potenza[2], and Kathleen Carroll[1]

[1]Yale School of Medicine, [2]Yale University

Background: Connectome-based modeling (CPM) is a machine learning method of generating behavioral predictions from neuroimaging data ('neural fingerprinting'). This study tested the ability of CPM to predict abstinence from cocaine in both a continuous and categorical manner, with out-of-sample replication.
Methods: Individuals with cocaine use disorder (CUD) were scanned before ($n=53$) and after ($n=40$) 12-week treatment. Whole-brain connectomes were created using standard methods. CPM with leave-one-out cross-validation was conducted to identify pre-treatment networks that predicted abstinence (percent cocaine-negative urines during treatment). Identified networks were then applied to post-treatment fMRI data to assess changes over time and in relation to abstinence during follow-up. Finally, the predictive ability of these networks was tested using data from an independent sample of individuals with CUD scanned prior to treatment ($n=18$).
Results: CPM predicted abstinence, as indicated by high correspondence between actual and predicted abstinence values ($p=0.001$). Identified networks included connections within and between canonical networks involved in attention/executive control (frontoparietal, medial frontal) and in reward responsiveness (subcortical, salience). Network strength assessed at post-treatment predicted abstinence during follow-up, in both a continuous and binary (i.e., treatment responder versus non-responder; 75% accuracy, $p=0.002$) manner. Network strength predicted treatment response in the independent sample with 67% accuracy alone and with 78% accuracy when combined with baseline cocaine-use ($p=0.03$).
Conclusions: These data demonstrate the ability of CPM to predict a complex, clinical outcome – abstinence from cocaine during 12-week treatment. They suggest that individual differences in connectivity contribute to variability in treatment response and may be an appropriate target for novel interventions.
Supported By: NIDA grants K01DA039299 and P50DA09241
Keywords: Cocaine Addiction, Prediction of Treatment Outcome, Connectome, Abstinence

SYMPOSIUM
From Astrocyte Functions to Behavioral Dysfunctions: Looking for Cellular Biomarkers of Distinct Neuropsychiatric Disorder

3:00 p.m. - 5:00 p.m.
Chair: Barbara di Benedetto
Co-Chair: Grazyna Rajkowska

81. Astrocytic EphB3 Receptors Control NMDA Receptor Functions

Valentin Langlais[1], Ines Benazzouz[1], Aurelie Jourdes[1], Illaria Belluomo[1], Isabelle Matias[1], Stéphane Oliet[1], and **Aude Panatier**[2]

[1]Inserm, [2]CNRS

Background: Astrocytes are key partners of neurons. One of their main functions is to regulate the activity of synaptic

NMDA receptors (NMDARs) through the supply of the coagonist D-serine. While this release occurs locally in a calcium and snare-dependent manner, the triggering mechanism leading to D-serine release from astrocytes is unknown. Interestingly, data in the literature obtained in astrocytes in cultures show that the activation of astrocytic EphB3 receptors increases D-serine availability. However, whether the interaction of this astrocytic receptor with its neuronal synaptic partner impact NMDAR functions is still unknown.
Methods: Experiments were performed on acute hippocampal slices from adult C57BL/6J mice. Levels of D-serine and NMDAR functions were studied respectively using capillary electrophoresis and electrophysiological recordings at hippocampal CA3-CA1 synapses.
Results: Here, we first established that the stimulation of EphB3 receptors led to an increase of D-serine availability (control, 100.0 ±10.8%, n=7; EphB3, 141.4 ±9.0%, n=6; $P<0.05$), inducing an increase of NMDAR activity (control, 104.5 ±3.9%, n=8; EphB3, 124.9 ±5.3%, n=10; $P<0.01$). These effects depended on astrocytes as EphB3 receptors activation had no impact on NMDAR activity when astrocytic calcium activity was inhibited (EphB3 activation control condition, 124.7±6.7%, n=6; EphB3 activation calcium-clamp condition, 96.1 ±5.0%, n=6; $P<0.01$). Second, inhibition of EphB3 receptors impaired NMDAR activity (control, 104.3 ±4.8%, n=8; EphB3, 81.3 ±5.3%, n=7; $P<0.05$). Finally, long-term synaptic potentiation was impaired when EphB3 receptor activation was inhibited (control, 138.7 ±7.1%, n=6; EphB3, 106.7 ±5.8%, n=7; $P<0.01$).
Conclusions: Our data indicate that astrocytic EphB3 receptors play a key role in NMDAR functions.
Supported By: FRM
Keywords: Astrocytes, Synaptic Transmission, NMDA Receptor, Long-Term Potentiation (LTP), EphB3

82. Astrocytic EphrinA Impacts the Distribution of Synaptic AMPA Receptors in Health and Depressive-Like Disorder

Victoria Malik[1] and **Barbara di Benedetto**[1]

[1]University of Regensburg

Background: Brains of major depressive disorder (MDD) patients show aberrant density and morphology of astrocytes and an altered glutamatergic activity in the prefrontal cortex (PFC), also present in an animal model of MDD, the high anxiety-related behavior (HAB) rats.
Methods: We investigated astrocytic dysfunctions in MDD using electrophysiology, microarray, chromatin-immunoprecipitation (ChIP), qPCR, immunofluorescent-immunohistochemistry and the forced swim test to measure depressive-like behaviors.
Results: Increasing the astrocytic ephrinA signalling in acute brain slices impairs long-term potentiation at glutamatergic synapses (N=4, $p<0.001$). This suggested a role of the astrocyte/neuron ephrinA/EphA system in MDD. Indeed, intracerebral injections of ephrinA1 induced a depressive-like behaviour in rats (N=10, $p<0.05$). Using ChIP/qPCR, we revealed an endogenously increased ephrinA1 expression in HAB primary astrocytes accompanied by an accumulation of the epigenetic mark H3K4me3 at its promoter (N=7, $p<0.01$). This was confirmed in PFC astrocytes of HAB rat brains (N=4, $p<0.001$). Because the ephrinA/EphA system modulates synaptic formation/function, we examined synapses in neurons co-cultured with either ephrinA1-enriched HAB astrocytes or with normal astrocytes. We observed no difference in total numbers of "silent" synapses, which corresponded to an unchanged relative enrichment of the AMPA receptor subunit GluR2 on total PSD95-positive spines. But we saw an increased relative number of "active" GluR1/PSD95-positive spines (N=3, $p<0.01$), which may indicate an altered homeostatic plasticity.
Conclusions: An increased astrocytic ephrinA1 expression may contribute to an altered synaptic structure which may induce MDD onset. A further exploration of its functional consequences might help to develop diagnostic tools or alternative therapeutic strategies for clinical interventions.
Supported By: Federal Ministry of Education and Research (BMBF, German), German Research Council (DFG)
Keywords: Astrocytes, ephrinA/EphA System, Major Depressive Disorder (MDD), Synapse, AMPA

83. Acute and Chronic Stress Models to Understand Pathophysiology of Psychiatric Disorders and Test Rapid-Acting Antidepressants

Laura Musazzi[1], Paolo Tornese[1], Nathalie Sala[1], and Maurizio Popoli[1]

[1]University of Milano

Background: Stressful life events represent a major risk factor for stress-related neuropsychiatric disorders.
Methods: We dissected the destabilizing effects of stress in the glutamate system and the consequences on brain structure/function. The footshock stress protocol is used as model of acute stress and the chronic mild stress protocol (CMS, 5 weeks) is used as model of chronic stress.
Results: Acute inescapable stress rapidly enhanced glutamate release/transmission in PFC, an effect sustained for 24 h (N=6; $P<0.001$). Unexpectedly, significant atrophy of apical dendrites was observed at 24 h, and sustained for at least 14 days. Chronic treatment with traditional antidepressants and single administration of ketamine (10 mg/kg) blocked the increase of glutamate release (N=8, $p<0.05$).

In rats subjected to CMS, ketamine was acutely administered to vulnerable (CMS-V) rats. Glutamate release was reduced in HPC synaptosomes from CMS-V (N=6, $p<0.05$). Significant reduction in expression of BDNF transcripts was found in all CMS rats. Reduced dendritic trafficking of BDNF mRNA and atrophy of apical dendrites was found in HPC of CMS-V. Ketamine treatment completely restored anhedonic behavior in CMS-V rats and most of the related changes, with the only exception of BDNF expression (N=8, $p<0.05$).
Conclusions: Acute and chronic stress induce typical signatures of behavioral, structural and functional changes, with overlapping features. Ketamine restores most maladaptive changes induced by stress. In particular, ketamine stabilizes the glutamatergic dysfunction in both cases, reducing

glutamate release enhanced by acute stress and restoring the reduction after CMS.

Our results suggest that ketamine could be used for prophylactic treatment in traumatic events.

Supported By: MIUR, Cariplo Foundation, EU, ECNP
Keywords: Stress, Glutamate, Ketamine, BDNF mRNA

84. Cerebral Organoids-Derived Astrocytes to Understanding Schizophrenia

Daniel Martins-de-Souza[1]

[1]University of Campinas (UNICAMP)

Background: Astrocytes are significantly involved in the pathophysiology of schizophrenia. They play vital roles brain tissue structure maintenance and integrity as well as aid neurotransmission. Despite all convincing evidences, we still lack in connecting all the molecular mechanisms underlying the role of astrocytes in schizophrenia.
Methods: We optimized a protocol to generate human functional astrocytes from cerebral organoids derived from human embryonic stem cells (hESC). Yielded cells were morphologically and functionally like astrocytes. Fifteen cerebral organoids from each lineage were mechanically dissociated and plated. This same protocol was then used to obtain astrocytes from cerebral organoids derived from hESC from 2 schizophrenia patients and 3 control subjects. These samples were submitted to mass spectrometry-based shotgun proteomic analysis. We considered proteins that were identified by at least 2 unique peptides with a false discovery rate $< 1\%$ (Benjamini-Hochberg adjusted). Quantified proteins were functionally annotated using Panther DB to identify ontological groups and protein-protein interactome was evaluated using STRING (minimum required interaction score was 0.7).
Results: The proteome of astrocytes revealed 3,048 proteins, with an overlap of 85.8% among all MS runs. We observed 148 differentially expressed proteins (ANOVA $p<0.05$), which significantly enriched 17 canonical pathways proteins (Panther:$p<0.05$). STRING-based interactive network representation revealed the following pathways with significant scores: glutamate receptor, cytokine-mediated inflammation, EGF, FGF and WNT signaling.
Conclusions: The generation of brain organoids-derived astrocytes holds great potential for the investigation of these cells in schizophrenia. This is a useful approach to drug screening and disease modeling, as supported by our proteomic results in schizophrenia cells.
Supported By: Sao Paulo Research Foundation (FAPESP).
Keywords: Proteomics, Astrocytes, Mass Spectrometry, Cerebral Organoids

SYMPOSIUM
Interdependent Metabolic and Inflammatory Mediators of Depressive Disorders in Animals and Humans

3:00 p.m. - 5:00 p.m.
Chair: Bruce McEwen

85. Brain Resilience for Mood Disorders: Role of Hormones and Neural Factors

Bruce McEwen[1]

[1]The Rockefeller University

Background: The brain is a plastic and vulnerable organ of the body. Experiences cause adaptive changes in dendrite length and branching, turnover of spine synapses and neurogenesis in the dentate gyrus region of the hippocampal formation. This adaptive plasticity is mediated by the excitatory amino acid neurotransmitter, glutamate, acting in concert with endogenous mediators such as neurotrophic factors, endogenous acetyl-L-carnitine (LAC) and other cellular messengers, along with circulating hormones.
Methods: Data for this plasticity and the role of circulating hormones and endogenous factors in this plasticity have used state of the art neuroanatomical, behavioral, cellular and molecular methods.
Results: Hormones of the metabolic, immune, gonads, thyroid gland and HPA axis participate in this plasticity leading to adaptation ("allostasis") but can also contribute to damage when overused and dysregulated among themselves resulting in "allostatic load/overload". Metabolic hormones are important, of which insulin and resistance to it in brain as well as the body leads to an inflammatory cascade and impaired cognitive function with increased risk for depression and dementia. Endogenous agents such LAC appear to play a role both centrally and systemically.
Conclusions: While the brain is capable of resilience from stressors including metabolic dysregulation, one cannot "roll back the clock". Instead, strategies are needed to intervene at different stages of the lifecourse to change the trajectory from negative to positive. Interventions to overcome impaired insulin signaling are particularly important to reduce the inflammatory cascade in the brain and prevent irreversible neurodegeneration as will become evident in the other presentations.
Keywords: Neuroplasticity, Mood Disorders, Insulin Resistance, Glutamate

86. Role of the Epigenetic Agent Acetyl-L-Carnitine as Gating Biomarker in Depression and Influences of Childhood Trauma

Carla Nasca[1], Betty Bigio[1], Francis Lee[2], Danielle Zelli[1], Sarah Young[3], Timothy Lau[1], Orna Issler[4], Caroline Menard[4], James Murrough[4], James Kocsis[2], Scott Russo[4], Eric Nestler[4], Natalie Rasgon[5], and Bruce McEwen[1]

[1]The Rockefeller University, [2]Weill Cornell Medical College, [3]Duke University, [4]Icahn School of Medicine at Mount Sinai, [5]Stanford University

Background: Converging preclinical evidence supports a role in depression for acetyl-L-carnitine (LAC), an epigenetic

modulator of central glutamatergic function with histone- and metabolic-enhancing properties.
Methods: Plasma LAC levels were determined in 71 patients with major depressive disorder (MDD) and 45 age/sex-matched HC using UPLC-MS/MS and ESI-MS/MS. The CTQ was used to assess stress experiences in childhood. In animals, chronic stress paradigms were used to test pro-resilient effects of LAC supplementation. Cell type specific viral gene expression was used to test for causal role of the glutamate receptor mGlu2 on depressive-like behaviors. Two-tailed t-tests, chi-square, and multiple regression were used as appropriate.
Results: LAC was lower in patients with MDD compared to HC($p<0.0001$,effect size=0.8). Of note, LAC was lower in patients who exhibited greater severity and earlier age-of-onset of MDD. Moreover, those patients with treatment resistant depression(TRD) had the greater reduction in LAC, and emotional neglect and being a female predicted decreased LAC($p=0.04$,$r=0.66$). In reverse translation studies, we found reduced expression of mGlu2 in the hippocampal ventral dentate-gyrus (vDG)($p<0.05$,$n=8$) in mice with depressive-like phenotypes, reduced LAC levels and insulin-resistance (elevated insulin and glucose). Neuronal mGlu2 overexpression in vDG($p<0.05$,$n=6$-8) or LAC supplementation($p<0.05$,$n=8$) promoted resilience.
Conclusions: Our new findings suggest that LAC may be a biomarker for a subtype of MDD. Mechanistically, LAC acts by modulating mGlu2 receptors in the hippocampus to promote resilience. Identifying the biological mediators underlying the interplay between metabolic dysfunction and depression can provide a target population for precision medicine and rational path forward for more effective therapeutic interventions.
Supported By: AFSP, HDRF, RTDF
Keywords: Glutamate, Epigenetic Biomarkers, Insulin Resistance, Histone Acetylation, Childhood History of Maltreatment

87. Social Stress Induces Neurovascular Pathology Promoting Immune Infiltration and Depression

Scott Russo[1], Caroline Menard[1], Madeline Pfau[1], Georgia Hodes[1], Veronika Kana[1], Victoria Wang[1], Sylvain Bouchard[2], Aki Takahashi[1], Meghan Flanigan[1], Hossein Aleyasin[1], Katherine LeClair[1], William Janssen[1], Benoit Labonte[3], Eric Parise[1], Zachary Lorsch[1], Sam Golden[1], Mitra Heshmati[1], Carol Tamminga[4], Gustavo Turecki[5], Matthew Campbell[6], Zahi Fayad[1], Cheuk Ying Tang[1], and Miriam Merad[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Albert Einstein, [3]Université du Québec Trois-Riviéres, [4]Ut Southwestern, [5]McGill University, [6]Trinity College

Background: Clinical studies suggest that heightened peripheral inflammation along with increased blood brain barrier permeability contributes to the pathogenesis of major depressive disorder.
Methods: We investigated the effect of chronic social defeat stress, a mouse model of depression, endothelial cell specific expression of tight junction protein claudin 5, blood-brain barrier (BBB) permeability and infiltration of peripheral immune signals. We also performed advanced confocal and electron microscopic assessment of blood vessel morphology along with functional dye injections assays to test BBB permeability. We utilized viral gene transfer to promote increased BBB permeability and test casual mechanisms increasing expression of depression-like behaviors.
Results: We found reduced expression of endothelial tight junction protein claudin-5 (cldn5) (ANOVA $n=6$-8 per group, $p<0.05$) and abnormal blood vessel morphology (ANOVA $n=3$, $p<0.05$) in nucleus accumbens (NAc) of stress-susceptible mice. CLDN5 expression was decreased in postmortem NAc of depressed patients (ANOVA $n=24$-26, $p<0.05$). Cldn5 knockdown increased stress-induced depression-like behaviors while chronic antidepressant treatment rescued cldn5 loss and promoted resilience (2-way ANOVA $n=8$-10, $p<0.05$). Reduced BBB integrity in NAc of stress-susceptible or cldn5 knockdown mice resulted in passage of peripheral proteins (ANOVA $n=7$-15, $p<0.05$) and subsequent expression of depression-like behaviors (2 way ANOVA $n=8$-10, $P<0.05$).
Conclusions: Greater understanding of the mechanisms by which chronic stress activates the immune system and undermines BBB integrity may promote the design of more effective antidepressant strategies, either by augmenting current treatment protocols or by informing the discovery of new therapeutics that enhance neurovascular health within stress-related brain regions.
Supported By: R01 MH104559, P50 AT008661
Keywords: Chronic Stress, Depression, Inflammation, Interleukin-6, Blood Brain Barrier

88. Allostatic Load Predictors of Treatment Response in Patients With Unremitted Depression

Natalie Rasgon[1], Katie Watson[1], Manpreet Singh[1], Tonita Wroolie[1], Alison Myoraku[1], and Siena Roat-Shumway[1]

[1]Stanford University School of Medicine

Background: Understanding the role of biomarkers of stress and allostatic load in prediction of antidepressant response is based on a fundamental biological premise of shortened life span as a result of environmental insults such as major somatic and psychiatric illnesses. Insulin resistance (IR), inflammation and telomere length are common mediators of allostatic load in depressive disorders. IR is a proinflammatory state and is in turn associated with oxidative stress. We studied leukocyte telomere length (LTL) as a predictor of antidepressant response to PPAR- ɣ agonist in patients with unremitted depression.
Methods: Forty-two subjects ages 23-71 with non-remitted depression participated in placebo-controlled add-on of pioglitazone to treatment-as-usual. Oral glucose tolerance tests were administered at baseline and at 12 weeks.

Results: At baseline, no differences in LTL were detected by depression severity, duration, chronicity or IR status. Subjects with longer telomeres exhibited greater declines in depression severity in active group, but not in placebo group, p=.005, r=-.63, CI 95%=(-0.84,-0.21). Depression severity decreased by an additional 1.5 points, β=-14.98, t(22)=-3.24, p=.005 for every .1 T/S longer LTL. LTL also predicted improvement in insulin sensitivity in the group overall but not between intervention arms, p=.036, r=-.44, CI 95%=(-0.74, 0.02) for the active arm, and p=.026, r=-.50, CI 95%=(-0.78,-0.03) for placebo.
Conclusions: LTL – a biomarker of allostatic load may emerge as a viable predictor of antidepressant response. An association between insulin sensitization and LTL regardless of the baseline IR status points to potential role of LTL as a non-specific moderator of metabolic improvement in these patients.
Keywords: Telomere Length, Insulin Resistance, Depressive Disorders, Stress and Allostatic Load, Inflammation

SYMPOSIUM
Towards Convergent Clinical Neuroscience: Integrating Genetics, Computation & Pharmacological Neuroimaging to Understand Psychosis Biomarker Mechanisms

3:00 p.m. - 5:00 p.m.
Chair: Alan Anticevic
Co-Chair: Joshua Gordon

89. Functional Connectivity Biomarkers of Psychosis in a Genetic High-Risk Population

Carrie Bearden[1], Charlie Schleifer[2], Amy Lin[1], Leila Kushan[1], Jie Lisa Ji[2], Genevieve Yang[2], and Alan Anticevic[2]

[1]University of California, Los Angeles, [2]Yale University

Background: Genetic and clinical heterogeneity present substantial challenges for elucidating causally relevant biomarkers for psychosis. 22q11.2 deletion syndrome (22q11DS) is a recurrent copy number variant (CNV) with high penetrance for psychotic spectrum disorders, and is thus an important translational model in which to investigate systems-level mechanisms implicated in idiopathic illness. Resting-state functional MRI (rs-fMRI) studies in schizophrenia have consistently revealed thalamic and hippocampal neural dysconnectivity. Here, we sought to test whether this circuitry is similarly disrupted in this genetic high-risk condition.
Methods: A sample of youth with molecularly confirmed 22q11DS (n=42) and demographically-matched healthy controls (n=39) were recruited and comprehensively phenotyped. Resting-state functional connectivity patterns Neuroimaging data were analyzed in line with the Human Connectome Project (HCP) pipeline. We computed functional relationships between individual-specific anatomically-defined thalamic and hippocampal seeds and all gray matter vertices.
Results: A significant group x seed interaction was observed (p<.001), indicating reciprocal disruptions in thalamic and hippocampal functional connectivity in 22q11DS patients relative to controls. Thalamo-cortical coupling was increased in 22q11DS in sensorimotor cortex, and reduced across associative networks. The opposite effect was observed for the hippocampus in regards to sensory and associative network connectivity.
Conclusions: Reciprocal thalamic and hippocampal dysconnectivity in 22q11DS suggest that high genetic risk for psychosis is linked with disruptions in large-scale cortico-subcortical networks, analogous to those observed in schizophrenia, those at clinical high risk for the illness, and in animal and pharmacological models of psychosis. These effects highlight the translational importance of highly penetrant CNVs for informing mechanisms underlying neural disruptions characteristic of idiopathic psychosis.
Supported By: NIMH R0129053, Simons Foundation
Keywords: Resting State Functional Connectivity, Copy Number Variant, Psychosis-Proneness, Biomarkers

90. Computational Modeling of Topographic Variation in Microcircuitry Across Human Cortex: Toward Linking Molecular Alterations With Neuroimaging Biomarkers

John Murray[1], Murat Demirtas[1], Joshua Burt[1], Lisa Ji[1], Katrin Preller[2], William Martin[3], and Alan Anticevic[1]

[1]Yale University School of Medicine, [2]University of Zurich, [3]BlackThorn Therapeutics

Background: Neuroimaging biomarkers for neuropsychiatric disorders and pharmacology exhibit spatial topographies, i.e., structured patterns across brain regions. A key computational challenge is to understand how such neuroimaging patterns emerge from underlying alterations in microcircuit function. Furthermore, development of pharmacological therapeutics may benefit from linking macrocircuit characterizations of neurobehavioral processes and pathologies to heterogeneous topographies of drug targets; this circuit-based approach can evaluate systemic pharmacological effects on "on-target" vs. “off-target” brain regions.
Methods: This presentation will introduce computational approaches to link transcriptomic maps, i.e., gene expression levels across brain regions, with neuroimaging measures. We analyzed spatial topographies of gene expression patterns in cortex using the Allen Human Brain Atlas (AHBA), in relation to neuroimaging maps of interest. We have also integrated maps of cortical heterogeneity into biophysically-based computational models of large-scale cortical dynamics applied to resting-state functional connectivity (rs-FC) neuroimaging data from the Human Connectome Project.

Results: Our AHBA analyses reveal cortical hierarchy provides an organizing principle for transcriptomic specialization across human cortex. In the large-scale model, hierarchical heterogeneity of microcircuit synaptic properties substantially increased the fit of the model to empirical rs-FC. Applying these computational approaches to pharmacological neuroimaging datasets, we found that cortical topography of gene expression can explain spatially heterogeneous effects of pharmacology on functional neuroimaging measures.
Conclusions: These studies provide computational frameworks for bridging across levels of analysis to test molecular and synaptic hypotheses through large-scale neuroimaging. Furthermore, they point toward understanding pharmacological effects and have the potential to guide the rational design of therapeutics targeted to specific brain circuits.
Supported By: NIH grants R01MH112746, R01MH108590, and TL1 TR000141; BlackThorn Therapeutics
Keywords: Computational Modeling, Resting-State, Transcriptomics, Pharmaco-fMRI, Computational Psychiatry

91. Investigating Molecular Homeostasis in Cortical Microcircuits in Health and Disease

Etienne Sibille[1]

[1]University of Toronto, CAMH

Background: Maintaining the balance between excitation and inhibition is a fundamental attribute of brain function that is necessary for information processing and higher functions, such as affect and cognition. This occurs through the fine-tuning of cells' functions to maintain optimal function. Hence, changes in gene function are likely to maintain long-term adaptations in the various cell types forming cortical microcircuits and may mediate maladaptive changes in brain disorders. We are testing this hypothesis at the cortical microcircuit level in various models, starting with brain aging in rodents.
Methods: Mouse behaviour (EPM, T-Maze), RNAscope, laser capture microdissection, RNAseq, bioinformatic analysis and computational modeling
Results: Old (22 months, n=12) male C57B6 mice displayed increased anxiety and reduced working memory compared to young mice (2 months, n=9; all Ps<0.05). RNA-seq from frontal cortex single cell types (pyramidal cells and PV+, SST+ and VIP+ interneurons; 100 cells/samples) revealed baseline cellular differences and distinct changes in age-related transcriptomes, pathway profiles, and structure of gene co-expression network, with modules correlating with behavioral dimensions in cell type-specific ways. The results suggest an order of neuronal vulnerability whereas age-related cellular activity changes affecting the different cells of frontal cortex microcircuit correlate with behavioral dimensions. Similar approaches are now being used in disease rodent models and in human samples from depression, bipolar depression and schizophrenia.
Conclusions: We will discuss how this dimensional approach across species, lifespan and brain disorders has the potential to reveal molecular mechanisms governing long-term homeostasis across the main cell types of brain cell microcircuits in health and brain diseases.
Supported By: CIHR
Keywords: Aging, Microcircuits, RNA Sequencing

92. Using Pharmacological Neuroimaging to Understand Microcircuit E/I Imbalance in Humans

Alan Anticevic[1], Charles Schleifer[1], Brendan Adkinson[1], Youngsun Cho[1], Peter Morgan[2], Aleksandar Savic[3], Murat Demirtas[2], Jie Lisa Ji[1], and John Murray[1]

[1]Yale University, [2]Yale University School of Medicine, [3]University of Zagreb

Background: Disruptions in excitation (E) and inhibition balance across cortical microcircuits has been implicated as a mechanism across neuropsychiatric disease, especially in schizophrenia spectrum disease. A way to test mechanisms behind putative E/I imbalance in humans involves leveraging pharmacological neuroimaging. One approach is to study the antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor and its effects on large-scale neural systems using data-driven functional connectivity.
Methods: We leveraged the NMDAR antagonist pharmacological model of schizophrenia by examining the effects of sub-anesthetic doses of ketamine on brain-wide functional connectivity in healthy volunteers (N=41). The data were collected using methods in line with the Human Connectome Project (HCP) and analyzed via the MSSM 1.0 Cortical Parcellation (i.e. the Glasser parcellation). We explicitly leveraged predictions from a whole-brain biophysically-based computational simulation of cortical circuit dynamics. The model incorporated a neurobiological-plausible 'gradient' of cortical recurrence via a proxy of cortical hierarchy - the human myelin map. This model generated key regional predictions for preferential effects across associative versus sensory circuits. We examined model and empirical effects via a data-driven global-brain connectivity (GBC) method.
Results: NMDAR antagonism preferentially elevated functional connectivity across 'higher order' associative cortex areas relative to sensory ones. This closely resembled prior observations in schizophrenia. The model and empirical effects were highly correlated across all sampled cortical parcels (r=0.5, p<0000.1).
Conclusions: Collectively, these results highlight a model implementation to capture change in GBC under acute ketamine administration. Empirically, the change in GBC shows hierarchy-related structure whereby effects were high in fronto-parietal networks but low in sensory networks.
Supported By: NARSAD Independent Investigator Grant; DP5-OD012109
Keywords: Ketamine, Schizophrenia, Computational Modeling, Functional connectivity, Data-Driven Analytics

Friday, May 11, 2018

PLENARY
Using Biomodels for Discovery
9:15 a.m. - 11:45 a.m.
Chair: Lori McMahon

93. Modeling Human Brain Development and Developmental Diseases Using HiPSCs

Guo-li Ming

Perelman School of Medicine University of Pennsylvania

Three dimensional (3D) cerebral organoid cultures from human iPSCs have been recently developed to recapitulate the cytoarchitecture of the developing brain. This system offers unique advantages in understanding molecular and cellular mechanisms governing embryonic neural development and in modeling congenital neurodevelopmental disorders, such as microcephaly. We have improved the organoid technology and developed a protocol to produce forebrain-specific organoids derived from human iPSCs using a novel miniaturized spinning bioreactor that recapitulate the human embryonic cortical development. ZIKV, a mosquito-borne flavivirus, has re-emerged as a major public health concern globally because ZIKV causes congenital defects, including microcephaly, and is also associated with Guillain-Barré syndrome in infected adults. We found that ZIKV exhibit specific tropism towards human neural progenitor cells and results in cell death and defects in neural development. I will discuss our recent work in further dissecting the molecular mechanisms underlying the ZIKV pathogenesis and microcephaly.

Keywords: Brain Organoids, Zika Virus, Human Brain Development

94. Microbiome Interactions With the Nervous System in Health and Disease

Elaine Hsiao

University of California, Los Angeles

The gut microbiota is emerging as an important modulator of brain function and behavior, as several recent discoveries reveal substantial effects of the microbiome on neurophysiology, neurogenesis, blood brain barrier permeability, neuroimmunity, brain gene expression and animal behavior. Despite these findings supporting a "microbiome-gut-brain axis", the molecular and cellular mechanisms that underlie interactions between the gut microbiota and brain remain poorly understood. To uncover these, the Hsiao laboratory is mining the human microbiota for microbial modulators of host neuroactive molecules, investigating the impact of microbiota-immune system interactions on neurodevelopment and examining the microbiome as an interface between gene-environment interactions in neurological diseases. We aim to dissect biological circuits for communication between the gut microbiota and nervous system, toward understanding fundamental biological pathways that influence brain and behavior.

Keywords: Gut Microbiome, Gene x Environment, Neurodevelopmental Disorders

95. From the Neural Circuits of Fear to the Neurobiology of PTSD

Kerry Ressler

McLean Hospital

The amygdala can be considered a 'hub' of emotional learning and memory. The amygdala, along with hippocampus and prefrontal cortex function have been consistently shown to be dysregulated in Posttraumatic Stress Disorder (PTSD). Furthermore, the neural plasticity that underlies associative learning, classical or Pavlovian conditioning, is relatively well understood, and the neural circuitry supporting threat or fear processing is among the most well-worked out circuits in behavioral neuroscience. In translation, fear-related disorders such as posttraumatic stress disorder, panic disorder and phobia manifest in ways that are consistent with an uncontrollable state of fear. Their development involves heredity, previous sensitizing experiences, association of aversive events with previous neutral stimuli, and inability to inhibit or extinguish fear, leading to a chronic and disabling state following from the initial learned fear event. In many ways, the 'over-learning of threats' or 'impaired extinction learning' related to fear processing can be considered central to these debilitating disorders.

I will highlight recent progress in the neurobiology of fear learning and memory, differential genetic susceptibility to disorders of fear, and how these findings are being applied to the understanding, treatment and possible prevention of fear-related disorders, such as PTSD. Promising advances are being translated from basic science to the clinic, including approaches to distinguish risk versus resilience before trauma exposure, methods to interfere with fear development during memory consolidation after a trauma, and techniques to inhibit fear reconsolidation and to enhance extinction of chronic fear. Cutting edge optogenetic and chemogenetic approaches to understand neural circuits and microcircuits, combined with the genetic and epigenetic regulation at a cell-type specific level within amygdala, medial prefrontal, and hippocampal circuitry as it relates to fear extinction will also be discussed. It is hoped that this new knowledge will translate to more successful, scientifically informed and rationally designed biomarker- and neurobiologically-driven approaches to disorders of fear regulation, including anxiety disorders and PTSD.

Keywords: PTSD

96. Genetic and Functional Genomic Investigation of Neuropsychiatric Disorders

Daniel Geschwind

UCLA

Dr. Geschwind will summarize work trying to leverage genetic findings and genomics to understand neuropsychiatric disease pathophysiology.
Keywords: Transcriptomics, Functional Genomics, Gene Networks

SYMPOSIUM
Biomarkers of Trauma, Stress, and Resilience in Substance Use Disorders
12:30 p.m. - 2:30 p.m.
Chair: Martin Paulus
Co-Chair: Jennifer Stewart

97. Relationships Among Substance Use Symptoms, Trauma History, and Levels of Neurocognitive Function for Females in a Criminal Diversion Program

Robin Aupperle[1], Rayus Kulplicki[1], Henry Yeh[1], and Martin Paulus[1]

[1]Laureate Institute for Brain Research

Background: Substance use disorder and trauma history are highly prevalent within incarcerated populations and are thought to play a role in recidivism. Clarifying relationships between comorbid symptomatology and various levels of neurocognitive function (e.g., neuropsychological performance, brain activation patterns) would be beneficial for informing psychoeducational and recovery-based interventions for these populations.
Methods: As part of an ongoing project, 67 women from a criminal diversion program completed substance use and trauma-related self-report measures, neuropsychological measures (assessing processing speed, attention, memory, and executive functions), and the monetary incentive delay task concurrent with fMRI (focused on ventromedial prefrontal (vmPFC), anterior cingulate (ACC), striatum, amygdala, and insula regions). Group factor analysis (GFA) was used to identify latent variables relating self-report, neuropsychological function, and reward processing. GFA aims to find factors capturing joint variability between data sets, explicitly modeling the independent variation within each data set.
Results: Preliminary GFA analyses identified six latent factors, each describing 4-13% of variance. Four were characterized by high factor loadings within only one block. One factor was characterized by higher loadings for trauma and substance use measures, and vmPFC, ACC, and amygdala responses to reward and loss. The last was characterized by higher loadings on trauma and substance use measures and neuropsychological variables (with variable directionalities of loadings).
Conclusions: These analyses demonstrate a novel approach to exploring relationships between multiple layers of neurocognitive function and symptomatology in comorbid populations. Preliminary results suggest that relationships between comorbid symptomatology and specific neurocognitive processes may be more robust than factors spanning different levels of neurocognitive function.
Supported By: William K. Warren Foundation
Keywords: Emotional Trauma, Substance Use, Reward Processing, Neuropsychology

98. Effects of Childhood Maltreatment on Neural and Biobehavioral Biomarkers of Relapse and Recovery in Substance Use Disorders

Rajita Sinha[1], Dongju Seo[1], Cheryl Lacadie[1], Todd Constable[1], and Gretchen Hermes[1]

[1]Yale University

Background: Childhood maltreatment (CM) is highly comorbid with Substance Use Disorders (SUDs), and significantly affects high relapse risk, but it's impact on relapse and treatment outcome are not well-understood. This presentation will focus on CM effects on neural and biobehavioral stress responses and their effects of SUD treatment outcome and relapse.
Methods: Participants include treatment engaged individuals with SUDs (N=58) and socially drinking controls (SD) (N=66) with and without CM, who participated in a functional neuroimaging (fMRI) study with prospective assessment of clinical outcomes for the SUD group. A previously validated brief sustained emotional provocation (SEP) task was utilized with block presentation of visual stress, alcohol/drug cues and neutral relaxing images in counterbalanced random order. Concurrent neural, subjective, autonomic and hypothalamic pituitary adrenal (HPA) axis responses were measured, and drug use outcomes were assessed during 8-weeks of outpatient treatment and a 90-day follow-up period.
Results: CM predicted high drug use during treatment and shorter time to relapse (p's$<$.05). Dynamic ventromedial prefrontal cortex (VmPFC) response during stress was associated with stress resilient coping in non-CM SDs ($p<.05$, whole brain corrected-WBC), but the CM+SUD group showed stress-induced blunted VmPFC ($p<.01$, WBC) and suppressed cortisol ($p<.05$) responses, that predicted greater substance use during treatment (r=-.54 and -.42, p's$<$.01) and higher propensity to relapse in those with CM+SUDS (p's$<$.05).
Conclusions: These findings indicate disrupted stress resilient neural and biobehavioral stress responses are potential predictive biomarkers of co-morbid CM and SUDs relative to the SUD group alone. Implications for novel therapeutics to target this CM+SUD pathophysiology will be presented.
Supported By: P50-DA016556; R01-AA013892; PL1-DA024859
Keywords: Childhood Maltreatment, Substance Use Disorder, Predictive Biomarkers, Hypothalamic-Pituitary-Adrenal Axis, Brain Imaging

99. Using a Multi-Modal Neuroimaging Approach to Track Abstinence-Mediated Recovery in Brain Structure and Function, Change in Cue-Reactivity and its Self-Regulation

Muhammad Parvaz[1], Nelly Alia-Klein[1], and Rita Goldstein[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Persistent deficits in the brain's structural and functional integrity characterize drug addiction. However, it is unclear whether these deficits recover with protracted abstinence in individuals with cocaine use disorders (iCUD).
Methods: Data from three different studies will be presented. The first study longitudinally quantified changes in brain structure and function using MRI and EEG techniques in 19 iCUD between baseline and 6-months follow-up. The second study cross-sectionally tracked drug-cue reactivity in 76 iCUD with varying abstinence duration (2-days, 1-week, 1-month, 6-months, and 1-year). The last study examined self-regulation of drug-cue reactivity in 37 iCUD using EEG and eye-tracking.
Results: At follow-up, compared to baseline, iCUD showed: 1) increased grey matter volume in the vmPFC and the left IFG (pFWE$<$.05), which correlated with improved Wisconsin Card Sorting Task performance (p=.003); 2) higher task activation in the midbrain (pFWE$<$.02), which correlated with reduced simulated cocaine choice (p$<$.001); 3) increased reactivity to pleasant pictures (p=0.03) but no difference in drug-cue reactivity. In the cross-sectional study, drug-cue reactivity revealed a parabolic inverted U-shaped trajectory with increasing abstinence duration (highest at 1- and 6-months; p=.002). Results further show that iCUD can self-regulate cue-reactivity (p=0.03), which in turn lowers the drug-cue-related attention-bias (p=0.02).
Conclusions: We show that psychophysiological and neuroimaging-based biomarkers can elucidate abstinence-mediated recovery in brain structure and function, a non-linear trajectory of drug-cue reactivity, and its self-regulation with associated spontaneous modulation of drug-cue-related attention-bias. These results call for development and application of more sophisticated neuroimaging methods to objectively track disease prognosis and treatment outcomes in drug addiction.
Supported By: NCATS: KL2TR001435 (Parvaz)
NIDA: R01DA023579, 1R21DA034954, and R01DA041528 (Goldstein).
Keywords: Cocaine Addiction, Craving, Abstinence, Recovery, Neuroimaging

100. Interaction of Drug Cues and Interoceptive Stress as a Function of Recovery From Methamphetamine Dependence: A Pilot Study

Jennifer Stewart[1], April May[2], Susan Tapert[2], and Martin Paulus[3]

[1]CUNY Queens College, [2]University of California, San Diego, [3]Laureate Institute for Brain Research; University of California, San Diego

Background: Amphetamine use disorder is characterized by attenuated prefrontal, anterior cingulate, and insular cortex processing during executive control and interoception. We investigated whether: (1) pairing of drug cues and interoceptive stress further compromises brain function in methamphetamine dependent (MD) users; and (2) this pattern changes as a function of recovery (remission). We hypothesized that current MD would exhibit lower stress-related frontocingulate and insular activation than remission MD and controls (CTL).
Methods: Current MD (n=11; ~2 weeks abstinent), remission MD (n=18; 12+ months abstinent), and CTL (n=10) viewed methamphetamine and neutral images while anticipating and experiencing interoceptive stress (breathing load) during functional magnetic resonance imaging (blocked design). Analyses included group as the between-subjects factor; image (methamphetamine, neutral) and interoception (anticipation, breathing load) as within-subject factors. Whole-brain exploratory analyses required individual voxel p$<$.05 with a cluster size $>$20 voxels.
Results: Across trials, both MD groups exhibited lower mid-insula/inferior frontal activation than CTL. During active stress (anticipation + breathing load − anticipation alone), both MD groups exhibited lower anterior insula/medial frontal activation than CTL, but current MD showed higher dorsal ACC activation than remission MD and CTL. During active stress to drug images (methamphetamine − neutral stress response), remission MD displayed higher superior/middle frontal activation than current MD.
Conclusions: Cross-sectional analyses indicate that insular changes are not associated with MD recovery within the context of interoceptive processing, although some frontocingulate regions appear to normalize as a function of long-term abstinence. Longitudinal designs are warranted to determine whether recovery produces brain changes to stress within an individual.
Supported By: UCSD Center on Interoceptive Dysregulation in Addiction (5P20DA027843)
Keywords: Interoception, Stimulants, Stress Reactivity, Recovery

SYMPOSIUM
The Cognitive Neuroscience of Reading Dysfunction in Schizophrenia
12:30 p.m. - 2:30 p.m.
Chair: Daniel Javitt

101. Dyslexics' Statistical Inference is Impaired Due to Fast Decay of Implicit Memory

Merav Ahissar[1] and **Sagi Jaffe-Dax**[2]

[1]Hebrew University, [2]Princeton University

Background: Dyslexics' difficulties are not limited to reading. They also often have difficulties in simple serial discrimination tasks. These difficulties can be largely explained as resulting from inefficient use of the experiment's stimuli statistics ("The Anchoring Deficit hypothesis", Ahissar et al., Nat Neurosci.

2006). We recently studied the neural basis underlying this behavioral manifestation and linked it with dyslexics' shorter stimulus-specific adaptation (Jaffe Dax et al., eLIFE, 2017).
Methods: We measured both behavioral use of statistics and ERP responses as a function of inter-trial-interval in control and dyslexic participants performing 2-tone frequency discrimination, finding that dyslexics' adaptation is shorter than controls'(ERP; Jaffe-Dax et al., 2017). We now replicated this experiment asking whether group-difference is manifested in the primary auditory cortex.
Results: We defined primary auditory cortex ROI in each hemisphere, and fitted a single exponential decay to the average BOLD response. We found significant differences between the groups' τs in the left auditory cortex (control: 17.6 sec, dyslexic: 9.6 sec, $z = 2.6$, $p < 0.01$, effect size $r = 0.42$. Mahn-Whitney U-test; Fig. 1C). In the right primary auditory cortex, the difference between controls' and dyslexics' τ had the same tendency, but was not significant (control: 11.3 sec, dyslexic: 8.3 sec, $z = 1.5$, $p = 0.15$, effect size $r = 0.23$).
Conclusions: Sensory cortical areas have different dynamics of adaptation in dyslexia, associated with reduced implicit memory. Future studies will indicate whether the same bottlenecks underlies impaired language skills in other populations.
Supported By: Israel Science Foundation
Keywords: Auditory Cortex, Statistical Learning, Brain Imaging, fMRI, Reading Disorder

102. Eye Movements and the Perceptual Span During Reading in Schizophrenia and Developmental Dyslexia: A Comparison

Veronica Whitford[1], Gillian O'Driscoll[2], and Debra Titone[2]

[1]The University of Texas at El Paso, [2]McGill University

Background: Although schizophrenia and dyslexia are clinically distinct disorders, both involve disrupted reading-related functions, including language processing and oculomotor control. Thus, reading may be similarly impaired in both conditions. Recently, we found that individuals with schizophrenia exhibited oculomotor markers of reading difficulty compared to matched controls, including slower reading rates, more regressions, and smaller perceptual spans (Whitford et al., 2013). Moreover, their perceptual span reductions were related to deficits in phonological processing and non-linguistic oculomotor control. Here, we examine whether adults with dyslexia also exhibit similar oculomotor markers of reading difficulty.
Methods: Following our 2013 study, 19 individuals with dyslexia and 17 matched controls read gaze-contingent moving window sentences, which manipulated the amount of parafoveal information rightward of fixation.
Results: Linear mixed-effects models revealed that the dyslexia group had slower reading rates, shorter forward saccades, more regressions, and extracted lower-quality information from the parafovea than controls, although the magnitude of their perceptual span (as classically defined) was comparable (~14 characters). Moreover, a comparison with the schizophrenia group ($n = 20$) tested in our 2013 study revealed no significant differences in all above-mentioned eye-movement measures, except perceptual span, which was significantly larger in the dyslexia group (~14 vs. ~6 characters). Further, unlike what was previously found in schizophrenia, deficits in phonological processing and non-linguistic oculomotor control did not relate to parafoveal processing in dyslexia.
Conclusions: Thus, individuals with schizophrenia and individuals with dyslexia exhibit both similarities and differences in their eye-movement reading behavior, which may reflect differential contributions of disrupted reading-related functions.
Supported By: Canada Research Chairs Program (Debra Titone); Stairs Memorial Foundation Fund (Debra Titone); National Sciences and Engineering Research Council of Canada Discovery Grant (Debra Titone: 204609); William Dawson Scholar award (Gillian A. O'Driscoll); Centre for Research on Brain, Language and Music
Keywords: Reading, Schizophrenia, Dyslexia, Eye Movements, Perceptual Span

103. Bottom-Up Processing During Natural Reading is Associated With Individual Differences in Phonological Awareness and Executive Control in People With Schizophrenia

Debra Titone[1], Veronica Whitford[2], and Gillian O'Driscoll[1]

[1]McGill University, [2]The University of Texas at El Paso

Background: Schizophrenia is characterized by neurocognitive disturbances that impact nearly all areas of functioning, including language. Most cognitive neuroscience work examining language in schizophrenia has focused on top-down contextual processing; however, recent work has revealed deficits in core bottom-up processes that underlie natural reading (reviewed in Whitford, O'Driscoll, & Titone, 2017).
Methods: Here, we present novel eye-tracking data for 20 people with schizophrenia and 19 controls from a naturalistic reading paradigm. Specifically, participants read paragraphs for comprehension in which all content words were coded for bottom-up difficulty (word frequency) and top-down difficulty (cumulative word predictability).
Results: Linear mixed effects models confirmed that across all eye movement measures (early measures such as gaze duration, late measures such as total reading time), people with schizophrenia exhibited deficits in bottom-up processing. This was evidenced by larger word frequency effects than controls (group x frequency interaction, $p < .05$), where people with schizophrenia were differentially slower for lower-frequency words. Moreover, word frequency effects in schizophrenia interacted with individual differences in phonological awareness, executive control, and clinical symptoms (all relevant interactions, $p < .05$). Lastly, unlike controls who exhibited top-down context effects across all reading measures, people with schizophrenia only exhibited such effects for early reading measures (i.e., gaze duration), though the group interaction was not significant.
Conclusions: These findings suggest that bottom-up language processes involved in natural reading are affected in

people with schizophrenia, and relate to underlying neurocognitive mechanisms associated with sound-based language processing and executive control.
Supported By: NSERC Discovery Award (Titone)
Keywords: Reading, Eye Tracking, Schizophrenia, Phonological Awareness, Executive Control

104. Neural Basis of Reading Dysfunction in Schizophrenia

Elisa Dias[1], Antigona Martinez[2], Gail Silipo[1], Anastasia Stoops[1], Ayelet Hochman[1], Matthew Hoptman[1], Nadine Revheim[1], and **Daniel Javitt**[2]

[1]Nathan Kline Institute, [2]Columbia University/Nathan Kline Institute

Background: Schizophrenia patients (SzP) show deficits in reading ability that compromise functional outcome. We have previously demonstrated that phonological contributions are related to impaired utilization of auditory tonal information and impaired auditory mismatch negativity generation. The present study evaluates visual/oculomotor contributions using a combined eye tracking/neurophysiology/fMRI/rsfMRI approach.
Methods: Data were obtained from 26 SzP and 26 healthy controls (HC) while they read passages of text. Eye-tracking measures included saccades/word, and fixation duration. Neurophysiological measures included fixation onset P1 ("lambda response") and alpha modulation. Task-based and resting-state fMRI (rsfMRI) evaluated integrity of functional connectivity within the reading connectome.
Results: SzP showed marked reduction in reading rate($d=1.3$, $p<.0001$) that reflected a decline from a prior higher level of function. Highly significant increases were observed in both the total number of saccades ($d=1.6$, $p<.0001$) and fixation duration ($d=.7$, $p=.026$). The increase in number of saccades correlated highly with impaired fixation-P1 generation ($r=.42$, $p=.004$), impaired visual contrast sensitivity ($r=.63$, $p<.0001$), and impaired functional connectivity within subcortical oculomotor control networks ($r=-.43$, $p=.007$) .
Conclusions: This study documents both “top down” and “bottom up” contributions to reading dysfunction in Sz. Top-down deficits involve frontal semantic networks and are primarily related to increased duration of individual fixations. Bottom-up deficits involve subcortical visual sensory and oculomotor control networks and primarily lead to a (dysfunctional) increase in saccade number. Fixation-P1 may serve as an objective index of low-level oculomotor dysfunction in Sz. Our findings are consistent with parallel research demonstrating impaired utilization of parafoveal information and NMDA receptor dysfunction, and demonstrate deficits within the reading connectome that lead to functional outcome impairments in Sz.
Supported By: R01 MH49334
Keywords: Schizophrenia, Reading Connectome, Early Visual Cortices, Visual perception, Semantic Association

SYMPOSIUM
Biomarkers in Schizophrenia: From Cellular and Molecular to Clinical Domains
12:30 p.m. - 2:30 p.m.
Chair: David Braff

105. Modeling the Contribution of Common Variants to Schizophrenia Risk

Kristen Brennand[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. Whereas highly penetrant variants have proven well-suited to human induced pluripotent stem cell (hiPSC)-based models, the power of hiPSC-based studies to resolve the smaller effects of common variants remains uncertain.
Methods: hiPSCs were reprogrammed from SZ patients and controls, subjected to CRISPR-based technologies to edit genotype or modulate gene expression, and differentiated into neurons for isogenic comparisons.
Results: We previously identified microRNA-9 as having significantly downregulated levels and activity in a subset of SZ hiPSC NPCs (four SZ and six control donors; 0.58-fold, $p=1.08e-07$, nested ANOVA), a finding that was corroborated by a larger replication cohort (ten SZ and ten control donors: 0.38-fold, $p=4.6e-04$, nested ANOVA) and further validated by an independent gene-set enrichment analysis ($p<0.001$) of the largest SZ genome-wide association study (GWAS) to date (rs181900, $p=7.1\times10-8$). Overall, this demonstrated a remarkable convergence of independent hiPSC- and genetics-based discovery approaches. In developing this larger case/control SZ hiPSC cohort (twelve SZ and twelve control donors; 94 RNA-seq) of hiPSC-derived NPCs and neurons, we identified a variety of sources of variation; reducing the stochastic effects of the differentiation process, revealed a concordance with two large post mortem datasets ($p<6.7x10-61$ and $1.6x10-20$).
Conclusions: We predict a growing convergence between hiPSC and post mortem studies as both approaches expand to larger cohort sizes. Altogether, our objective is to understand the cell-type specific contributions of SZ risk variants to disease predisposition.
Supported By: Brain and Behavior Young Investigator Grant, National Institute of Health (NIH) grants R01 MH101454 and R01 MH106056 and the New York Stem Cell Foundation.
Keywords: Schizophrenia, Stem Cells, CRISPR, Neurons

106. Genome-Wide Significant Locus on Chromosome 5 Influences Psychosis Risk and General Intellectual Ability

David Glahn[1], Andrew McIntosh[2], Assen Jablensky[3], Vishwajit Nimgaonkar[4], Ruben Gur[5], Joanne Curran[6], Laura Almasy[5], Raquel Gur[5], and John Blangero[6]

[1]Yale University, [2]University of Edinburgh, [3]University of Western Australia, [4]University of Pittsburgh School of Medicine, [5]University of Pennsylvania, [6]South Texas Diabetes and Obesity Institute, University of Texas Health Science Center at San Antonio & University of Texas of the Rio Grande Valley

Background: Endophenotypes are that subset of biomarkers that are related to the genetic liability for an illness. Reduced general intellectual ability (g) has been consistently associated with genetic risk for psychotic disorders, particularly, schizophrenia, based on twin and family analyses and based on polygenetic risk scores in unrelated individuals. However, the gene or genes that influence both intellectual functioning and psychosis risk are currently unknown.
Methods: Using four separate pedigree-based samples (total n=1489 individuals from 259 families) that included psychiatric diagnoses and neurocognitive assessments, we searched the genome for chromosomal regions jointly influence both traits. An index of g was derived for each sample separately reflecting the first principal component of a factor analysis including a wide variety of neuropsychological measures.
Results: Using SOLAR, the heritability of g was estimated for each sample (h2=0.47-0.96, all $p<0.05$). A locus on chromosome 5 was genome-wide significantly linked (lod scores ranged from 2.9-7.5) to intellectual functioning in 3 of the 4 samples. Secondary analyses indicated that the same locus influenced risk for psychosis in all four samples. Finally, formal bivariate models were significant for three of four samples.
Conclusions: Together, these analyses indicate that a locus on chromosome 5 likely harbors a gene or genes influencing risk for g and psychosis. Currently, we are interrogating whole genome sequence data within this locus.
Supported By: NIH/NIMH U01 MH105630
Keywords: Psychosis, General Intellectual Ability, Linkage, Chromosome 5

107. Genome-Wide Association of Endophenotypes for Schizophrenia From the Consortium on the Genetics of Schizophrenia (COGS) Study

Tiffany Greenwood[1], Laura Lazzeroni[2], Monica E. Calkins[3], Robert Freedman[4], Michael F. Green[5], Raquel E. Gur[3], Ruben C. Gur[3], Gregory Light[1], Keith Nuechterlein[6], Ann Olincy[4], Allen Radant[7], Larry Seidman[8], Larry Siever[9], Jeremy Silverman[9], William Stone[8], Catherine Sugar[6], Neal Swerdlow[1], Debby Tsuang[7], Ming Tsuang[1], Bruce Turetsky[3], and David Braff[1]

[1]University of California, San Diego, [2]Stanford University, [3]University of Pennsylvania, [4]University of Colorado, [5]VA Greater Los Angeles Healthcare System, [6]University of California, Los Angeles, [7]University of Washington, [8]Harvard Medical School, [9]Icahn School of Medicine at Mount Sinai

Background: We have previously reported our efforts to characterize the genetic architecture of 12 heritable endophenotypes for schizophrenia in the COGS-1 family sample. Candidate gene association and genome-wide linkage results converge on a single network related to glutamate signaling. We now report genome-wide association results for these endophenotypes in an independent cohort of schizophrenia cases and controls.
Methods: PsychChip genotypes were obtained for 1729 subjects. Through the PGC pipeline, we applied standard quality control filters, confirmed ancestry, and imputed >6M variants with a genotyping rate >0.99. The final datasets included 1029 European subjects and 183 Latino subjects from COGS-2, and 321 European controls from COGS-1. Association was performed using linear regression, adjusting for age, sex, and five principal components from each dataset with results combined through weighted meta-analysis.
Results: Initial analyses identified 5 independent regions exceeding standard genome-wide significance thresholds for 4 endophenotypes: the antisaccade task, degraded stimulus Continuous Performance Test, abstraction and mental flexibility, and spatial processing. Many independent regions exceeding a genome-wide suggestive threshold of 1E-5 were also identified for all 12 endophenotypes.
Conclusions: These analyses have identified many genomic regions of interest that require further exploration and validation in the 1093 COGS-1 family members and 1034 COGS-2 cases and controls of African ancestry. It is important to note that we are investigating the genetic architecture of heritable neurocognitive and neurophysiological endophenotypes associated with schizophrenia risk. Understanding the molecular basis of these endophenotypes, many of which are recognized as treatment targets by the FDA, will pave the way for precision based medicine.
Supported By: National Institute of Mental Health
Keywords: Schizophrenia, Endophenotypes, Genome-Wide Association Study, Genetics, Cognition

108. Consolidation Across Multiple Levels of Analysis for Parsing Biological Heterogeneity in Psychosis

Brett Clementz[1], Ana Stan[2], Godfrey Pearlson[3], John Sweeney[4], Matcheri Keshavan[5], Carol A. Tamminga[6], and Robert Gibbons[7]

[1]University of Georgia, [2]UT-Southwestern, [3]Olin Neuropsychiatry Research Center, Institute of Living, Yale University, School of Medicine, [4]University of Cincinnati, [5]Harvard Medical School, [6]University of Texas Southwestern Medical Center, [7]University of Chicago

Background: For psychosis, work at only one level of analysis may yield incomplete answers to pressing questions. RDoC formalizes appreciation for levels of analysis, and encourages integrating theories from genes to molecules to circuits to physiology to behavior. Work at only one level of analysis may lead to incomplete, perhaps incorrect, answers to our pressing questions.
Methods: B-SNIP is a multisite project investigating the neurobiological and clinical heterogeneity of psychosis. For this presentation, 3T sMRI, smooth pursuit eye movements, and clinical features were collected. Structural MRIs were quantified using Freesurfer and smooth pursuit data were quantified to obtain measures of pursuit onset and maintenance using established procedures. A combination of Item Response Theory and canonical correlation approaches were used to analyze data across levels of analysis.

Results: Compared to over 300 healthy persons, sMRI deviations were widespread across multiple cortical and subcortical structures in over 800 psychosis cases ($p<.001$). When considered by associations with other variables, a more orderly picture emerged. Psychosis clinical features (delusions, hallucinations, paranoia, passive/apathetic social withdrawal, depression, unusual thought content) track with tempo-parietal junction-inferior frontal sMRI deviations ($p<.01$) but smooth pursuit eye movement deficits tracked with parietal motion processing and superior frontal sMRI deviations ($P<.01$) in the same subjects. One relationship did not account for the other.
Conclusions: Structural MRI deviations are not a unitary phenomenon and did not account equally for variations at other levels of analysis, suggesting either pleiotropy across all psychosis or etiological heterogeneity that is not captured by current approaches to psychosis subtyping.
Supported By: NIMH MH077851, MH078113, MH077945, MH077852, and MH077862
Keywords: Psychosis, MRI, Smooth Pursuit, Classification, Heterogeneity

SYMPOSIUM
Emerging Epigenetic Pharmacotherapy: Focus on HDACs and Cognition
12:30 p.m. - 2:30 p.m.
Chair: Claes Wahlestedt

109. HDAC3 Regulation of Circadian Gene Per1 Mediates Age-Dependent Memory and Synaptic Plasticity

Marcelo Wood[1]

[1]University of California, Irvine

Background: The focus of this presentation is on the role of HDAC3 in regulating circadian gene expression during memory consolidation in the young and aging brain. We have been testing the hypothesis that chromatin structure is in a repressive state in specific areas of the genome in the aging brain, which negatively affects gene expression required for memory formation.
Methods: The approach involves a combination of genetically modified mice, adeno-associated viruses (AAVs) to generate focal deletions of HDAC3 or express mutant forms of HDAC3 in the dorsal hippocampus, and lastly, we use HDAC3 selective inhibitors as a third approach to manipulate HDAC3 function. We use behavioral tasks to assess memory and also examine long-term potentiation, a form of synaptic plasticity, in the dorsal hippocampus. Additional methods include immunofluorescence, RT-qPCR, ChIP-qPCR, RNAseq, and CRISPR/dCas9.
Results: We have found that a focal deletion of histone deacetylase 3 (HDAC3) in the aging brain ameliorates age-dependent memory impairments and synaptic plasticity deficits. Focal deletion of HDAC3 in the hippocampus restores circadian gene expression, which correlates with improved cognition. Furthermore, inhibiting expression of PER1 only in the hippocampus leads to significant memory impairments in the young brain, and overexpressing PER1 in the aging brain ameliorates age-dependent memory impairments.
Conclusions: Together, the results indicate that HDAC3 may be misregulating expression of PER1 and circadian gene expression in the hippocampus, which leads to age-related memory and synaptic plasticity impairments. The results also suggest that PER1 may have an autonomous role in memory beyond its known role in regulating circadian rhythms.
Supported By: NIH-NIA
Keywords: Epigenetics, Memory Consolidation, Synaptic Plasticity, Circadian Rhythms, Hippocampus

110. Epigenetic Treatments for Dementia: HDAC Inhibitors & Beyond

Stephen Haggarty[1]

[1]Massachusetts General Hospital & Harvard Medical School

Background: Frontotemporal dementia (FTD) is a clinical syndrome, characterized by progressive deterioration of decision-making abilities, control of behavior, and language. A frequent cause of FTD is loss-of-function mutations in the GRN gene encoding progranulin (PGRN), a secreted glycoprotein with growth factor-like and immunomodulatory activities. One potential strategy to correct the pathological consequences of GRN haploinsufficiency is to increase the expression from the remaining functional allele. To this end, inhibitors of histone deacetylases (HDACs), have been shown to be induce PGRN expression. However, the precise molecular mechanisms behind their regulation of PGRN, including if they directly affect histone acetylation within the GRN locus, which HDACs are the relevant targets, and their optimal kinetic profile, has yet to be elucidated.
Methods: We established a human iPSC-based neuronal culture system with robust and scalable mRNA and protein level assays and assembled a collection of small-molecule probes differentially targeting HDACs, including opto-epigenetic probes enabling control of HDAC activity by light.
Results: Our data provide strong evidence to support the conclusion that inhibition of Class I HDACs is sufficient to enhance PGRN protein production. We further show that only HDAC inhibitors with apparent fast-on binding to their target HDACs are capable of potently enhancing GRN mRNA expression. We also linked changes in GRN mRNA induction to changes in histone acetylation in the GRN promoter.
Conclusions: This work provides an example of leveraging advances in epigenetic drug discovery to develop disease-modifying treatments for genetic forms of dementia, which may be relevant for a broader set of neuropsychiatric disorders, including bipolar disorder.
Supported By: Bluefield Project to Cure FTD, MGH Research Scholars Program
Keywords: Epigenetic, Dementia, Human Neural Stem Cells

111. Synaptic Vesicle Glycoprotein 2A (SV2A) Levels as a Translatable Measure of Synaptic Density Following HDAC Inhibition

Magnus Ivarsson[1], Maria Quinton[1], Berkley Lynch[1], Timothy McKee[1], Nathan Fuller[1], and Adam Rosenberg[1]

[1]Rodin Therapeutics

Background: Disruptions of dendritic spines are reported for many CNS diseases and are closely related to cognitive impairment. In patients with Alzheimer's disease (AD), synapse loss in the hippocampus is strongly correlated with cognitive deficits. There is a growing realization that epigenetic regulation through histone deacetylases (HDACs) play a role in synaptic function and plasticity. HDAC2 overexpression in mice has been shown to decrease spines, synapses and cause cognitive impairment; the opposite is observed in HDAC2 knockout mice. In addition, cognitive deficits have been shown to be attenuated following treatment with HDAC inhibitors.
Methods: One principle challenge in understanding any potential beneficial role of improving synaptic density in neurological disorders has been the lack of tools to quantify changes in synaptic density in a clinical setting. Synaptic vesicle glycoprotein2A (SV2A) is a membrane protein found in presynaptic terminals and is essential for synaptic function. Recently, it has been demonstrated that you can quantify synaptic density in human subjects by PET imaging of SV2A.
Results: Rodin has demonstrated that the prototypic HDAC inhibitor, CI-994 significantly and dose-dependently increased dendritic spine numbers in the hippocampus in wild type mice following 14-days of oral administration (one-way ANOVA;n=5-7/group;$p<0.05$). The increase in spine density was accompanied by a significant increase in the synaptic levels of SV2A. We have also shown that sub-chronic CI-994 administration improved LTP-deficits in the 5xFAD AD mouse model.
Conclusions: Together these findings strongly support that SV2A measurements would be a viable translational approach to study the pro-synaptic effects of HDAC inhibitors in a clinical setting.
Supported By: SBIR
Keywords: HDAC Inhibitors, SV2A, Dendritic Spines

112. Multipronged HDAC Strategy for Alzheimer's Disease

Claude-Henry Volmar[1], Hasib Salah-Uddin[1], Karolina J. Janczura[1], Paul Halley[1], Guerline Lambert[1], Andrew Wodrich[1], Sivan Manoah[1], Nidhi H. Patel[1], Gregory C. Sartor[1], Neil Mehta[1], Nancy T.H. Miles[1], Sachi Desse[1], David Dorcius[1], Michael D. Cameron[2], Shaun P. Brothers[1], and Claes Wahlestedt[1]

[1]Miller School of Medicine, University of Miami, [2]Scripps Florida

Background: None of the FDA-approved Alzheimer's disease (AD) treatments address the main hallmarks of the disease. With the recent clinical trial shortcomings of AD immunotherapy as well as γ- and β-secretase inhibitors among others, we and colleagues agree that a multifactorial approach is needed to address the polygenicity of AD. We used an epigenetic strategy where a single drug would simultaneously affect the expression of well-defined AD-related targets.
Methods: AD-related genes and proteins were analyzed using NanoString technology, RT-qPCR methods, Western blots and ELISAs (N = 3 to 6). Behavioral effects on the 3xTg AD mouse model was assessed using the open field, the Y-maze, the Barnes Maze and the novel object recognition tests (N=10). Unpaired Student's T-test was used whenever only two means were being compared. One-way ANOVA or repeated measures two-way ANOVA with appropriate post hoc analyses were used for multiple comparisons.
Results: The HDAC inhibitor M344 reduces Aβ(1-42) accumulation ($p<0.05$), decreases tau Ser396 phosphorylation ($p<0.01$), and increases the expression of several high-priority AD-related protective genes. M344 normalizes late-onset risk factor AD genes such as APOEe4 ($p<0.0001$) and BIN1 ($p<0.0001$). M344 also results in reversal of cognitive impairment in the 3xTg AD mice. M344 shows low toxicity, and rapidly clears out of brain and plasma.
Conclusions: Our data suggest that a small epigenetic molecule with brief daily brain exposure can target the non-amyloidogenic pathway, increase neuroprotective genes, show low toxicity and increase memory in an AD model. This work endorses a shift to a multitargeted approach to the treatment of AD.
Supported By: Grants 5AZ09 and 6AZ08 (to C.W.) by the Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Program; NIH Grants 4R01DA035055-05 and 5R01AA023781 (to C.W.); NIH Grants 1R01MH110441 and 1R01NS092671 (to S.P.B.).
Keywords: Epigenetics, Multitargeting Approach, HDAC Inhibitors, Alzheimer's Disease, Beta-amyloid

SYMPOSIUM
Bridging the "Causality Gap" in Human Psychiatric Neuroscience
12:30 p.m. - 2:30 p.m.
Chair: Amit Etkin

113. Brain Lesions Associated With Depression are Characterized by a Unique Pattern of Brain Connectivity

Michael Fox[1]

[1]BIDMC/Harvard Medical School

Background: Focal brain lesions can lend insight into the causal neuroanatomical substrate of depression; however, studies of lesion location alone have led to inconsistent results.
Methods: Here, we use three datasets with different lesion etiologies and measures of depression (N = 276), along with maps of human brain connectivity from a large normative dataset (N = 1000), to address this question in a unique way. Each lesion volume was transformed to a common brain atlas and the functional connectivity profile of each lesion location was computed.
Results: We found that lesion location itself was highly heterogeneous, and lesion location alone was not significantly associated with depression. However, functional connectivity between the lesion location and the left dorsal lateral prefrontal cortex (DLPFC) was significantly associated with depression ($p < 0.0001$). Negative functional connectivity (anticorrelation) to the right nucleus accumbens and septal nuclei was also predictive ($p < 0.05$). Positive frontal connectivity and negative limbic connectivity were independent predictors of

lesion-induced depression and were consistent across lesion type, dataset, depression metric, and time point.
Conclusions: These results lend insight into the causal substrate of depression symptoms, identify patients at risk for post-stroke depression, and may help refine treatment targets for techniques like brain stimulation.
Supported By: R01MH113929, R21MH099196, K23NS083741, Nancy Lurie Marks Foundation
Keywords: Depression, Stroke, Lesion, Brain Connectivity, Functional Connectivity

114. A "Circuits First" Approach to Mental Illness

Amit Etkin[1]

[1]Stanford University

Background: Progress in psychiatry has been hampered the non-specific nature of psychiatric diagnoses, the limited arsenal of effective treatments, and the correlative nature of neuroimaging. We therefore need a more direct and causal linkage between circuit dysfunction and clinical presentation and treatment outcome.
Methods: I will present on studies using fMRI, concurrent TMS/fMRI and concurrent TMS/EEG, covering depression and PTSD. Studies include: a sham-controlled study of repetitive TMS (rTMS) for depression, a wait-list controlled study of psychotherapy for PTSD, and cross-sectional investigations of PTSD in two independent cohorts.
Results: In depression, better clinical outcome with rTMS treatment is seen in patients for whom the function (at rest or as measured by TMS/EEG stimulation probes) of the prefrontal target for rTMS was more perturbed. In PTSD, we found that otherwise symptomatically indistinguishable patients can be divided into two broad categories based on behavior and resting-state fMRI connectivity, and that this predicts outcome with psychotherapy. Moreover, connectivity was correlated with TMS/EEG evoked responses at specific prefrontal locations. Finally, using concurrent TMS/fMRI we found a prefrontal region which can causally regulate amygdala activity, that this causal influence was deficient in PTSD, and that disrupting its function in healthy individuals led to PTSD-like behavioral changes.
Conclusions: These findings suggest a path forward towards a circuit-based approach for diagnosis and treatment in psychiatry, centered primarily around tools for mapping causal influence in brain circuits (i.e. TMS/EEG, TMS/fMRI) that transcends the arbitrariness and heterogeneity of traditional diagnoses, the limitations of group-level imaging analyses and current trial-and-error approaches to treatment planning.
Supported By: NIH R01 MH103324 and DP1 MH116506, and grants from Cohen Veterans Bioscience and the Stanford Neurosciences Institute
Keywords: TMS-EEG, TMS-fMRI, PTSD, Depression, Brain Connectivity

115. Neuroimaging Biomarkers Predicting Distinct Subtypes of Anhedonic Behavior in Depression

Conor Liston[1]

[1]Weill Cornell Medical College

Background: Biomarkers have transformed modern medicine but remain largely elusive in psychiatry, partly because there is a weak correspondence between diagnostic labels and their neurobiological substrates.
Methods: We used statistical clustering and machine learning methods to discover novel subtypes of depression based on distinct patterns of altered connectivity in limbic and frontostriatal networks, as indexed by resting state fMRI in a large multisite sample (N=1,188 subjects).
Results: Clustering patients on this basis enabled the development of biomarkers (statistical classifiers) for diagnosing depression subtypes with high (82-93%) sensitivity and specificity in multisite validation (N=711, $p<0.001$) and out-of-sample replication (N=477, $p<0.001$) datasets. I also will present unpublished results of an effort to further improve this approach to subtyping and investigate how altered connectivity in specific circuits contributes to specific depression-related behaviors. In particular, I will show 1) how regularized canonical correlation analysis can be used to identify a sparse subset of connectivity features that are robust to overfitting in relatively small datasets and predict distinct forms of anhedonic behavior in an effort-based decision making task ($p<0.005$); and 2) how the acute BOLD signal response to TMS targeting these circuits can be used to predict subtype-specific improvements in anhedonia and related depressive symptoms after repeated TMS ($p<0.001$ in cross-validation).
Conclusions: These results show how distinct patterns of altered connectivity in frontostriatal networks predict different forms of anhedonic behavior in novel neurophysiological subtypes of depression, which in turn predict differing antidepressant responses to rTMS.
Supported By: R01 MH109685, Rita Allen Foundation, Dana Foundation, One Mind Institute, Klingenstein-Simons Fellowship in Brain Science
Keywords: Depression, Biomarkers, rsfMRI, Anhedonia

116. Distinctive Mechanisms of Action for DLPFC-, DMPFC-, and OFC-rTMS in Major Depression

Jonathan Downar[1], Peter Fettes[1], Katharine Dunlop[1], Sarah Peters[1], Fidel Vila-Rodriguez[2], Peter Giacobbe[1], Zafiris Daskalakis[3], and Daniel Blumberger[3]

[1]University of Toronto, [2]The University of British Columbia, [3]Centre for Addiction and Mental Health

Background: Conventional diagnostic approaches in psychiatry are categorical; more recent approaches identify transdiagnostic domains of pathology, with underlying neural substrates. Recent evidence suggest that certain resting-state functional networks may be transdiagnostic substrates of pathology across multiple psychiatric disorders. These networks are potential targets for interventions such as repetitive transcranial magnetic stimulation (rTMS). A personalized approach to rTMS would target different networks to address different domains of pathology in each individual patient.
Methods: We review clinical and neuroimaging findings from 120 adults with medication-resistant unipolar major depression who underwent a 30-session course of rTMS targeting either left dorsolateral prefrontal cortex(DLPFC), bilateral dorsomedial prefrontal cortex(DMPFC), or right orbitofrontal cortex(rOFC). All

patients underwent T1 and 10 min rs-fMRI neuroimaging 1 week before and after treatment, in addition to behavioral-task and clinical assessments(HamD17,BAI). Seed-based ROI analyses identified predictors and correlates of response.
Results: At a conservative whole-brain familywise error $p<0.01$, distinctive predictors and correlates were apparent for DLPFC-,DMPFC- and rOFC-rTMS. For DLPFC-rTMS($n=50$), subgenual cingulate connectivity to ventromedial PFC predicted and correlated to improvement. For DMPFC-rTMS($n=40$), dorsal anterior cingulate connectivity to dorsal striatum predicted/correlated to improvement. For rOFC-rTMS($n=30$), midbrain dopaminergic-ventral striatal connectivity correlated to improvement. Behavioral tasks revealed improved flanker-task performance as a mediator of improvement for DLPFC- and DMPFC-rTMS, versus normalized sensitivity to negative feedback on reversal-learning for rOFC-rTMS. rOFC-rTMS more potently improved anxiety and suicidal ideation, versus DLPFC-rTMS.
Conclusions: DLPFC-,DMPFC- and rOFC-rTMS may target distinctive domains of pathology via distinctive neural mechanisms in depression. Personalized approaches, matching patient symptoms to stimulation targets, could improve overall treatment outcomes.
Supported By: CIHR, Brain Canada, Edgestone Foundation
Keywords: rTMS, Resting State fMRI, MDD, Personalized Medicine, Biomarkers

SYMPOSIUM
Novel Insights Into the Functional and Molecular Correlates in Identifying Suicidality
12:30 p.m. - 2:30 p.m.
Chair: Yogesh Dwivedi

117. Neurodevelopment of Suicidal Behavior in Bipolar Disorder

Elizabeth Lippard[1], Fei Wang[2], Maria Oquendo[3], and **Hilary Blumberg**[2]

[1]UT Austin, [2]Yale University School of Medicine, [3]University of Pennsylvania

Background: It is estimated 50% of individuals with bipolar disorder (BD) will attempt suicide and 15-20% will die by suicide. Adolescence/young adulthood is a critical period during which suicide behavior often manifests. In this talk, a model for the development of suicidal ideation and behavior during adolescence/young adulthood, and cross-sectional and longitudinal multimodality neuroimaging data to support the model, will be presented.
Methods: Multimodality magnetic resonance imaging (MRI) (structural MRI, diffusion tensor imaging and functional MRI) and multidimensional symptom and behavioral assessments were performed for adolescents/young adults with BD ($n=68$, 38% who had made at least one suicide attempt), and healthy control (HC) ($n=45$) at baseline and approximately 3 years later.
Results: Adolescents/young adults with history of attempts showed baseline decreases in ventral frontotemporal system gray matter volume, white matter structural integrity and functional connectivity ($p<0.001$). Greater magnitude of these decreases at baseline were observed in adolescents who made a future suicide attempt following their baseline assessment, compared to those who did not ($p<0.001$). In assessing longitudinal within-subject repeat scans, the interim attempters also showed altered ventral frontotemporal system changes over time. Regional brain circuitry differences were associated with symptoms and behaviors, including suicidal ideation severity and attempt lethality ($p<0.05$).
Conclusions: Taken together, the findings support involvement of ventral frontotemporal corticolimbic system abnormalities, and developmental trajectory differences, in risk for and the development of suicide-related symptoms and behaviors in adolescents/young adults with BD. Implications for brain circuitry and mechanisms to target to reduce risk and prevent suicide will be discussed.
Supported By: NIMH, AFSP, IBF, BBRF
Keywords: Suicide Attempts, Suicide Risk Factors, Bipolar Disorder, MRI, Diffusion Tensor Imaging (DTI)

118. Single-Cell Transcriptome of the Depressed and Suicidal Brain

Corina Nagy[1], Malosree Maitra[1], Jean-Francois Theroux[1], Haig Djambazian[1], and **Gustavo Turecki**[1]

[1]McGill University

Background: Brain molecular changes are typically measured in tissue homogenates. However, multiple neuronal and glial subtypes with specific gene expression patterns are likely to be distinctly modified in a diseased state. The detection of subtle transcriptomic alterations such as those expected in psychiatric, would benefit greatly from single cell resolution.
Methods: Using post-mortem brain tissue we conducted single-cell (single-nuclei) transcriptome analysis in 16 individuals who died by suicide during an episode of major depression and 16 matched healthy controls. Bulk nuclei were isolated from BA8/9 using an Optiprep™ gradient and single nuclei were captured using 10x Genomics' Chromium technology, a droplet based protocol. The tagged libraries were sequenced using Illumina's HiSeq 4000 platform to approximately 40-50k reads per nucleus. We used a custom Cell Ranger pipeline to produce a gene barcode matrix. Downstream bioinformatics analysis was performed by Seurat.
Results: Using Seurat to perform unsupervised clustering, we are able to produce well define clusters that can be classified by differential expression of board markers of cell type. Transcriptional profiles were used to further subdivided into clusters for differential analysis between groups. Random forest plots produced differential cluster profiles between groups.
Conclusions: These data are the stepping stone for identifying cell-specific genes and networks of genes whose expression is dysregulated in depression.
Supported By: CIHR foundation grant
Keywords: Major Depressive Disorder (MDD), Single Cell Type Sequencing, Transcriptomics, Human Postmortem Brain

119. Functional Assessment of an Attempted Suicide Risk Locus

Virginia Willour[1] and **Marie Gaine**[1]

[1]University of Iowa Carver College of Medicine

Background: We previously conducted an attempted suicide genome-wide association study in subjects with bipolar disorder that generated a strong association signal on 2p25 (5.07 X 10-8). The top SNPs localize to a 10kb region that we now know contains 30 novel putative microRNAs.
Methods: We used CRISPR-Cas9 genome editing in HEK293 cells to delete the 10 kb region (n=4 deleted and 4 control cell lines). mRNA-based RNA-Seq was used to determine if any genes were differentially expressed in the deleted samples. We then compared our 10kb deletion RNA-Seq data to our suicidal behavior whole exome and genome-wide methylation datasets and to our lithium treatment expression datasets to identified overlapping candidate genes and pathways.
Results: Analysis of the RNA-Seq data showed that the 10kb deletion influences the regulation of 37 genes, with the strongest effect on DNAJC15 (corrected p-value 3.20E-34), a mitochondrial protein import gene that promotes apoptosis. Comparison to our other datasets indicated that we had an overlap with the lithium studies, where our top two lithium-responsive genes were HSPA1A (corrected p-value = 1.56x10-29) and HSPA1B (corrected p-value = 3.71x10-26), both of which are HSP70 heat shock proteins that act to inhibit apoptosis.
Conclusions: DNAJC15, HSPA1A, and HSPA1B are predicted to interact with one another – with opposing effects on apoptosis - and are expressed in brain regions (such as the cerebral cortex) of relevance to suicidal behavior. While this converging evidence is intriguing, much work needs to be done to determine the relevance of these findings in the mammalian brain.
Supported By: NIH R01 MH079240
Keywords: Suicide, RNA Sequencing, Bipolar Disorder, CRISPR

120. miRNA Network Reorganization in dlPFC and its Contribution to Suicidal Behavior

Yogesh Dwivedi[1]

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Background: MicroRNAs (miRNAs) are one of the most important epigenetic modifiers that belong to non-coding RNA family with a precise epigenetic role to modulate the coding potential of transcribed mRNA pool based on characteristic sequence complementarity. The present study examined the contribution of miRNAs in the reorganization of gene expression networks in dlPFC of suicide subjects.
Methods: miRNAs in dlPFC of suicide (n=25) and healthy subjects (n=25) were determined by miRNA sequencing. SAM analysis was used to analyze significant differences in individual miRNAs. miRNAs were also analyzed by miRNA sequencing in synaptonerosomes. Igraph package in R was used analyze pairwise co-expression relationships where nodes represent miRNAs and edges connect pairs of miRNAs. Target genes were analyzed with IPA core analysis module for functional enrichment of target genes using Fisher Exact Test and P-value $\leqslant 0.05$.
Results: We found differential alterations in expression of 29 miRNAs in dlPFC of suicide subjects ($p<0.01$). Many of them were synaptically enriched and encoded at nearby chromosomal loci, shared motifs within the 5'-seeds, and shared putative mRNA targets. In addition, we found a dramatic reorganization of miRNAs in a coordinated and cohesive fashion in suicide subjects which was not present in healthy control group. Synaptically enriched miRNAs were highly associated with this reorganization.
Conclusions: Our findings show that miRNAs contribute substantially to a reorganization of gene expression network that occurs in suicide. Affected miRNAs are likely to participate in pathogenesis of suicide via altering the expression of mRNAs that regulate synaptic plasticity.
Supported By: R01MH082802; 1R01MH101890; R01MH100616; 1R01MH107183
Keywords: microRNA, Suicide, Dorsal Lateral Prefrontal Cortex, Network, Human Postmortem Brain

SYMPOSIUM
Large-Scale Neuroimaging in Psychiatric Diseases: Cross-Modality, Cross-Disorder Comparisons From ENIGMA's International Studies

12:30 p.m. - 2:30 p.m.
Chair: Paul Thompson

121. Biological Insight From Large-Scale Studies of Bipolar Disorder With Multi-Modal Imaging and Genomics

Ole Andreassen[1], Josselin Houenou[2], Edouard Duchesnay[2], Pauline Favre[2], Melissa Pauling[2], Neeltje van Haren[3], Rachel Brouwer[3], Sonja de Zwarte[3], Paul Thompson[4], and Christopher Ching[5], ENIGMA Bipolar Disorder Working Group

[1]University of Oslo, [2]NeuroSpin Neuroimaging Platform, & INSERM, IMRB, APHP, CHU, [3]Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, [4]Imaging Genetics Center, Keck School of Medicine, University of Southern California, [5]Neuroscience Interdepartmental Program, UCLA, USC

Background: Bipolar disorder (BD) affects 1-3% of adults worldwide, but its pathophysiology and genetic underpinnings are still poorly understood. By using harmonized processing and analysis protocols, The ENIGMA Bipolar Disorder Working Group (BDWG) is increasing the power and replicability of neuroimaging studies of BD. Here we present recent findings from the BDWG including machine learning classification of diffusion data, and a large-scale study of unaffected first-degree relatives of patients with BD.

Methods: Thirty-three international samples comprised of 2,767 BD and 4,056 healthy controls (HC) were processed using ENIGMA structural and DTI processing protocols. Machine learning consisted of supervised (support vector machine) learning techniques to perform BD versus HC classification as well as subgroup classification within BD using DTI measures. Global and subcortical brain measures for 805 first-degree relatives of BD patients were compared to HC by meta-analysing linear mixed modeling results through the ENIGMA Relatives Group.
Results: Moderate, but significant, accuracy was reported for supervised BD versus HC classification (AUC=0.62; Sensitivity/Specificity 0.63/0.61). First-degree relatives of BD subjects showed significantly larger brain measures in general compared to HC, including higher intracranial volume, cortical and cerebellar gray matter, total brain surface area, as well as ventricle volumes.
Conclusions: The machine learning analysis of neuroimaging markers in BD is the largest to date, and future work aims to combine DTI with structural, fMRI, and genomic data to improve classification. Alterations in first-degree relatives of BD subjects may suggest the presence of genetic vulnerability or even resilience in particular brain structures involved in the development of BD.
Supported By: U54 EB020403
Keywords: Bipolar Disorder, Multimodal Neuroimaging, ENIGMA Consortium, Unaffected First-Degree Relatives, Machine Learning

122. Convergent Brain Mechanisms in 22q11.2 Deletion Syndrome and Schizophrenia

Christopher Ching[1], Daqiang Sun[2], Julio Villalon Reina[3], Kenia Martinez[4], Rachel K. Jonas[5], Amy Lin[5], Leila Kushan[2], Theo van Erp[6], Jessica Turner[7], ENIGMA Schizophrenia Working Group, Paul M. Thompson[8], and Carrie Bearden[2], ENIGMA 22q11.2 Deletion Working Group

[1]UCLA, [2]Semel Institute for Neuroscience and Human Behavior; University of California-Los Angeles, [3]Imaging Genetics Center, University of Southern California, [4]Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Universidad Europea de Madrid, [5]UCLA School of Medicine, Semel Institute for Neuroscience and Human Behavior, [6]University of California, Irvine, [7]Georgia State University, [8]Imaging Genetics Center, Keck School of Medicine, University of Southern California

Background: 22q11.2 deletion syndrome (22q11DS) is a recurrent copy number variant associated with greatly elevated risk for psychosis. The ENIGMA 22q11.2 Deletion Syndrome Working Group (22qWG) represents the largest neuroimaging consortium effort to study 22q11DS and its relationship to psychosis. Here, in conjunction with the ENIGMA Schizophrenia Working Group (SZWG), we investigated overlap between cortical, subcortical, and diffusion-tensor imaging (DTI) markers of 22q11DS and schizophrenia.
Methods: ENIGMA harmonized image processing methods were applied to brain MRI data from 11 international data collection sites (22q11DS=523; healthy controls=349). Multiple linear regression models were used to assess overall group differences in morphology and DTI indices. Regional effect size differences between age- and sex-matched 22q11DS subjects with and without psychotic disorder (22q11DS+Psy vs. 22q11DS-Psy) were tested against case-control results from the SZWG (N>9,000).
Results: Thinner cortex in frontal, temporal, and parietal regions was associated with 22q11DS+Psy, which significantly overlapped with thinner regions in schizophrenia cases relative to controls. Ranked cortical effect size results from 22q11DS+Psy were significantly correlated with those from the SZWG (r=0.48, p=3.7x10-5). Smaller hippocampal and thalamic volumes were associated with 22q11DS+Psy, consistent with comparisons between schizophrenia and controls. DTI analysis revealed that a significant proportion of 22q11DS+Psy exhibited lower diffusivity than 22q11DS-Psy, in line with findings from SZWG, where schizophrenia was associated with widespread reductions in diffusivity.
Conclusions: While 22q11DS overall is associated with complex brain alterations, convergence between 22q11DS+Psy and idiopathic schizophrenia indicates that 22q11DS serves as a valuable model for studying the pathophysiology of psychosis, particularly in high-risk individuals prior to symptom onset.
Supported By: RO1 MH085953 and U54 EB020403
Keywords: Multimodal neuroimaging, 22q11 Deletion Syndrome, Schizophrenia, ENIGMA Consortium, Clinical High-Risk States for Psychosis

123. Brain Structure, Disease Risk, and Common Genetic Variation

Neda Jahanshad[1], Genetics working group ENIGMA Consortium

[1]University of Southern California

Background: Ten years ago, there was limited knowledge of any specific genetic factors underlying many complex human traits. The lack of power and reproducibility failures were particular obstacles in psychiatry and in studies of brain structure. Large-scale global consortia have formed to search genome-wide to identify common genetic variants that comprise the basic biological core of the brain and its diseases. In the last year, these efforts from hundreds of researchers around the world have shown remarkable payoffs. While the PGC has identified variants that contribute to disease risk, the ENIGMA consortium has identified loci that shape subcortical/cortical structure. Independent of genetics, ENIGMA has also identified consistent diseases effects in human brain structure, in global populations. The connections among genetic variation, brain structure, function, and disease, can finally be investigated.
Methods: In GWASs of N~35-40,000, the underlying genetic structure of approximately 80 cortical/subcortical phenotypes have been mapped. Genetic loci that show increased risk for schizophrenia, BP, MDD, ADHD, and Alzheimer's among others have also been identified. Using tests of genetic correlation and overlap, we identify the genetic relationship between brain variance and risk for disease, and show how these relate to findings of brain differences between patients and controls.
Results: Significant genetic correlations exist between global brain surface area and risk for ADHD ($r_g = -0.1$, $p < 10-3$),

between superior frontal area and risk for schizophrenia (r_g =0.2, p < 10-4), between hippocampal volume and Alzheimer's (r_g =-0.15, p < 10-3).
Conclusions: A network of genetic correlations exists between brain structure and disease risk.
Supported By: U54 EB020403
Keywords: Brain Imaging, Genetics, Psychiatric Disease

124. Large-Scale Machine Learning and Neuroimaging in Psychiatry

Paul Thompson[1]

[1]University of Southern California

Background: Machine learning approaches are increasingly used for analyzing psychiatric research data. Within ENIGMA, working groups studying 10 different psychiatric disorders are now applying machine learning methods to discover new patterns in neuroimaging, clinical, demographic and genetic data. We summarize progress in these efforts across multiple disorders; we note several surprises and challenges in creating predictive models that generalize well across diverse populations; we also present new work merging information from thousands of patients across multiple centers to create predictive models that generalize well.
Methods: One such project, by the ENIGMA MDD group, identified MRI features that best distinguish patients with major depressive disorder, by fusing information from 16 different cohorts, including structural MRI scans of 3,237 participants (1,826 healthy controls and 1,411 with MDD). Adopting two machine learning methods, we examined classification accuracies across cohorts, and the effects of using different approaches and cohort combinations to train the classifier.
Results: Performance varied widely across sites (64.9-97.9%), with optimal results for MDD patients with recurrent episodes or on antidepressants. The hippocampus, orbitofrontal cortex, insula, and anterior cingulate were consistently identified across analyses, pointing to the role of distributed perceptual and reward-based learning networks in MDD.
Conclusions: Machine learning approaches can fuse imaging biomarkers to distinguish patients from controls. Different machine learning methods had different strengths and limitations; some successes were gained making predictive models robust to different data acquisitions.
Supported By: NIH U54 EB020403
Keywords: MRI, Brain Imaging, Machine Learning, MDD, Classification

SYMPOSIUM
Prenatal Stress and Fetal Programming of Health and Disease Risk: Role of Epigenetic Mechanisms and Telomere Biology
12:30 p.m. - 2:30 p.m.
Chair: Annamaria Cattaneo

125. Hippocampal Progenitor Cell Models in Deciphering the Epigenomics of Stress

Nadine Provencal[1], Janine Arloth[2], Annamaria Cattaneo[3], Christoph Anacker[4], Torsten Klengel[5], Carmine M. Pariante[6], and Elisabeth Binder[2]

[1]Simon Fraser University, [2]Max Planck Institute of Psychiatry, [3]IRCCS Fatebenefratelli Brescia, Institute of Psychiatry, King's College, London, [4]Columbia University, [5]McLean Hospital/Harvard, [6]Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College, London

Background: Exposure to early life stress (ELS) is a well-known major risk factor for developing psychiatric and behavioural disorders later in life. A growing body of evidence indicates that exposure to ELS can lead to long lasting changes in a number of systems including the endocrine system, the immune system and brain structure and function. However, our understanding of the mechanisms underlying these effects is limited. One proposed mechanism that might lead to some of these long-lasting effects is that excessive glucocorticoids (GC) release after ELS exposure induces long-lasting epigenetic alterations in important regulatory genes. Accumulating evidences suggest that epigenetic mechanisms are in part responsible for the embedding of ELS.
Methods: We used human hippocampal progenitor cells (HPCs) exposed to GCs during neurogenesis and multi-omic data analysis integrating gene expression and DNA methylation (5mC) at a genome-wide level to assess the long-lasting effects of GCs.
Results: We identified long-lasting 5mC alterations induced by GCs exposure during neurogenesis (FDR < 0.1), where a significant portion of these marks were maintained after neuronal differentiation. The sites showing GC-induced methylation changes are enriched in regulatory regions as well as in genes differentially methylated during fetal brain development and in genes previously associated with child abuse in human hippocampus and blood cells. To some extent, they also reflect epigenetic changes induced by acute GCs exposure in human blood cells.
Conclusions: Together, these results suggest that GC-induced epigenetic alterations in HPCs might reflect GC actions during ELS and be in part responsible for the increased risk for psychopathology.
Supported By: NARSAD
Keywords: Epigenetic, DNA Methylation, Hippocampal Progenitor Cell, Glucocorticoids, Early Life Stress

126. Prenatal Depression Exposure and Enhanced Stress Responses in the Offspring: Role of the Glucocorticoid-Mediated Epigenetic Changes

Annamaria Cattaneo[1], Chiara Malpighi[1], Nadia Cattane[2], Nadine Provencal[3], and Carmine Pariante[4]

[1]Biological Psychiatry Lab, IRCCS Fatebenefratelli Brescia, [2]IRCCS Fatebenefratelli, [3]Simon Fraser University and Child & Family Research Institute, CANADA, [4]King's College London, Institute of Psychiatry

Background: Depression in pregnancy represents a vulnerability risk factor for the development of offspring vulnerability to develop adverse experiences, such as victimization, enhanced emotional reactivity, difficult temperament and poor emotional and cognitive regulation in childhood. Up to now, the molecular mechanisms mediating the long-lasting effects of

depression exposure in utero have not been identified yet, however, they may involve epigenetics.
Methods: We have measured cortisol saliva levels by using ELISA technique and saliva DNA methylation signatures by using 450K Arrays both in women characterized for depression in pregnancy and their babies at different time points (6 days after birth, 8 weeks and one year). Behavioural evaluations have been performed in babies by using Neonatal Behavioural Assessment Scale, and Bayley Scales of Infant Development.
Results: We will show how both depressed women as well as their babies have an increase in saliva cortisol levels, indicating over-activity of stress response system. These stress related alterations are associated with babies' behavioral dysregulation, including being birth less alert ($U=1038.5$; $Z=-3.8$; $p<.001$), more irritable ($U=1151.5$; $Z=-2.7$; $p=.007$), more difficult to be assessed by the examiner ($U=1279.5$; $Z=-2.5$; $p=.012$) and poorer in motor maturity ($U=1318$; $Z=-2.4$; $p=.018$). These long lasting molecular and behavioural alterations, observed in babies, were associated with changes in DNA methylation.
Conclusions: Here we provide some mechanistic pathways responsible of the development of persistent molecular and behavioral alterations in babies exposed to depression in utero; if targeted, we may prevent the transmission of depression, and the associated negative outcomes, from mothers to infants.
Supported By: RC to Cattaneo
Keywords: Maternal Depression, Stress Reactivity, Epigenetics, Altered Behaviour in Offspring

127. The Epigenetic Clock at Birth: Associations With Maternal Antenatal Depression and Child Psychiatric Problems

Anna Suarez[1], Jari Lahti[1], Darina Czamara[2], Marius Lahti[1], Anna Knight[3], Polina Girchenko[1], Esa Hämäläinen[4], Eero Kajantie[5], Hannele Laivuori[1], Pia Villa[1], Rebecca Reynolds[6], Alicia Smith[7], Elisabeth Binder[2], and **Katri Räikkönen**[1]

[1]University of Helsinki, [2]Max-Planck Institute of Psychiatry, [3]Emory University, [4]HUSLAB, Helsinki University Central Hospital, [5]National Institute for Health and Welfare, [6]University of Edinburgh, [7]Emory University School of Medicine

Background: Maternal antenatal depression may compromise the fetal developmental milieu and contribute to individual differences in aging and disease trajectories in later life. We evaluated the association between maternal antenatal depression and a novel biomarker of aging at birth, namely epigenetic gestational age (GA) based on fetal cord blood methylation data. We also examined if this biomarker could prospectively predict early childhood psychiatric problems.
Methods: 694 mothers from the PREDO Study provided information on history of physician-diagnosed depression before pregnancy,581 completed the Center for Epidemiological Studies Depression Scale biweekly throughout pregnancy, and 407 filled in the Child Behavior Checklist at child's age 3.7 ($SD=0.75$) years. DNA methylation (DNAm) GA of fetal cord blood DNA was based on the methylation profile of 148 selected CpGs. Epigenetic GA was calculated as the arithmetic difference between DNAm GA and chronological GA and adjusted for chronological GA in linear regression models.
Results: Maternal history of physician-diagnosed depression (Mean difference=-0.25 SD units, 95%CI -0.46;-0.03, $p=0.03$) and greater depressive symptoms throughout pregnancy (-0.08 SD unit per SD unit, 95%CI -0.16;-0.01, $p=0.04$) were associated with lower child's epigenetic GA. Lower child epigenetic age, in turn, prospectively predicted total behavioral, internalizing, emotionally reactive, and withdrawn problems in boys.
Conclusions: Maternal antenatal depression is associated with epigenetic GA immaturity in offspring. Epigenetic GA immaturity seems to be developmentally disadvantageous for boys, who in early childhood show greater psychiatric problems in maternal reports.
Supported By: Academy of Finland, University of Helsinki
Keywords: Epigenetic Biomarkers, Maternal Depression, Neuropsychiatric Symptoms

128. Prenatal Stress and Telomere Biology

Sonja Entringer[1]

[1]Charite Universitätsmedizin Berlin

Background: The long-term consequences of exposure to excess stress on the initiation and progression of many age-related diseases are well established. The effects of stress are particularly salient if exposure occurs during sensitive developmental windows such as intrauterine life and the early postnatal period (i.e., the concept of fetal or developmental programming of health and disease). The elucidation of mechanisms underlying such effects is an area of intense interest and investigation. We propose that the integrity of the telomere system represents a candidate system of particular interest in this context.
Methods: Data will be presented from several different cohorts in which intrauterine conditions (including obstetric risk conditions, maternal stress- and nutrition-related processes) were assessed, and telomere length (TL) was measured in newborns, infants and adults. In one of the cohorts, data from child follow-up assessments regarding temperament, developmental milestones and behavior problems were available.
Results: Maternal psychosocial stress during pregnancy is associated with offspring TL in two independent cohorts in newborns ($p<0.05$, $n=27$) and adults ($p<0.05$; $N=94$). Furthermore, a pro-inflammatory maternal milieu during pregnancy is associated with reduced newborn TL ($p<0.05$, $N=103$). Newborn TL, in turn, is associated with child behavioral problems related to attention deficit hyperactivity disorder (ADHD) at 3.5 years age ($p<0.05$, $N=515$).
Conclusions: Taken together, our findings provide evidence in humans that stress-related processes during pregnancy may exert a programming effect on the newborn and infant telomere biology system.
Supported By: R01 AG-050455, R01 HD-060628, R01 HD-065825, ESR 678073
Keywords: Telomere, Prenatal, Stress

SYMPOSIUM
Stress, Anxiety, and Depression: HPA Axis Disruption in Fear, Memory, and Mood Neural Circuits

12:30 p.m. - 2:30 p.m.
Chair: Scott Langenecker
Co-Chair: Jennifer Blackford

129. HPA and Amygdala CRH Alterations Associated With Primate Anxiety

Ned Kalin[1]

[1]University of WI School of Medicine and Public Health

Background: Studies in new born monkeys followed longitudinally over the first year of life examine the developmental trajectory of threat-induced cortisol in relation to individual differences in the development of anxiety and its underlying neural circuitry. Additional studies in preadolescent monkeys test the role of amygdala CRH systems in mediating anxiety.
Methods: A longitudinal design studying 35 rhesus monkeys over the first year of life was used with behavioral phenotyping, multimodal neuroimaging, and cortisol analyses. In preadolescent monkeys, a viral vector strategy using real time MRI intraoperative infusions was used to overexpress CRH in the dorsal amygdala.
Results: In preadolescent monkeys, over expression of dorsal amygdala CRH resulted in increased anxiety ($p<.05$) that was associated with increased metabolism in components of the anxiety circuit, including the amygdala, posterior OFC and brain stem ($p<.05$). In addition, during the first year of life the association of cortisol with developmental trajectories in the structure and function of the neural circuitry underlying anxiety was determined.
Conclusions: These findings define the relation between individual differences in early life cortisol and the development of individual differences in anxiety and its underlying neural circuit. Additionally, these studies provide a proof of concept for "gene therapy" studies in primate species and directly implicate increased amygdala CRH gene expression in the development of pathological anxiety.
Supported By: R01MH046729; P50MH100031
Keywords: HPA, CRH, Anxiety, Development, Primate

130. Neuroendocrine and Neural Markers of Anxiety Vulnerability in Children

Jennifer Blackford[1], Jacqueline Clauss[2], Adaora Mgboh[1], Uma Rao[3], and Margaret Benningfield[1]

[1]Vanderbilt University Medical Center, [2]Massachussets General Hospital, [3]University of California, Irvine

Background: Identifying neural correlates of anxiety vulnerability will provide critical information about the pathophysiology of anxiety disorders. It has been proposed that hyper-responsivity to stress may one mechanism underlying anxiety risk. In the present study, we investigated cortisol and neural markers of stress sensitivity with anxiety vulnerability in children.
Methods: Psychiatrically healthy 8-10 year olds (n=39) were recruited represent a range of from low to high anxiety vulnerability. Cortisol was densely sampled over two weekend days (n=10) and during the scan (n=3) to provide: waking, awakening response, bedtime, and scan habituation measures of cortisol. Brain activity (ALFF) was measured in the amygdala and BNST. ANOVAs were performed.
Results: Child-report of anxiety vulnerability was predicted by the amygdala ALFF X cortisol awakening response ($p = .01$). In children with low to moderate awakening responses, anxiety vulnerability was positively correlated with amygdala activity at rest; however, for children with robust awakening responses, anxiety vulnerability was negatively correlated with amygdala activity. Parent-report of anxiety vulnerability was predicted by the interaction of amygdala ALFF X cortisol habituation during the scan ($p = .003$). In the children who showed a typical pattern of cortisol habituation, higher amygdala activity was correlated with higher anxiety vulnerability. However, in children with a sustained cortisol response across the scan, anxiety vulnerability was predicted by lower amygdala activity.
Conclusions: These data provide evidence for a brain-cortisol relationship in children at high-risk for developing anxiety, before the onset of disease, pointing an important signature of anxiety risk.
Supported By: F30-MH097344; T32-MH018921, T32-GM07347; UL1-TR000445
Keywords: Anxiety, At-Risk Youth, Functional Neuroimaging, Cortisol

131. Anticipatory Cortisol Modulation of Memory, Affective Processing, and Resting-State Networks During fMRI in Mood Disorders

Amy Peters[1], Lisanne Jenkins[2], Leah Kling[1], Kelly Ryan[3], Anne Weldon[4], Jonathan Stange[1], Katie Bessette[1], Monica Starkman[3], Melvin McInnis[3], Jon-Kar Zubieta[5], Robert Welsh[5], Sara Weisenbach[5], and Scott Langenecker[1]

[1]University of Illinois at Chicago, [2]Northwestern University, [3]University of Michigan, [4]University of Illinois, [5]University of Utah

Background: The neural networks involved in stress-related HPA-axis reactivity and emotion perception, memory, and intrinsic network function overlap. However, direct links between neuroendocrine and cognitive/affective neural systems are understudied in mood disorders (MD).
Methods: Two independent samples provided (anticipatory) salivary cortisol before fMRI. First, pre-scan cortisol and its interaction with disease (active; aMD [n=39] vs. HC [n=23]) were predictors of activation during Semantic-cue List Memory and Facial Emotion Processing (whole-brain corrected [WBC] $p<.01$). Second, resting state fMRI, with cortisol and cortisol by disease predictors, of bilateral seed-based connectivity analyses from the DMN (posterior cingulate, hippocampus) and the SEN (amygdala, subgenual anterior cingulate) were

tested in remitted MD (rMD; n=73) and HC (N=47); WBC p<.01.
Results: During emotion processing, pre-scan cortisol levels predicted increased engagement of fronto-parietal and striatal regions in HC; this association was inverted in aMD. For memory, pre-scan cortisol positively predicted fronto-limbic activation during encoding in HCs, but hypoactivation in aMD. During resting-state, pre-scan cortisol predicted diffuse decreases (HC) and increases (rMD) in within-and cross-network relationships, notably of the dorsal anterior cingulate/medial PFC, DLPFC, brain stem/cerebellum (all seeds) and precuneus (DMN seeds).
Conclusions: Anticipatory cortisol levels reflect prominent individual differences for healthy subjects, effects that are inverted with disease in task-based and resting state analyses. The effects of cortisol are widespread, but coalescence around dorso-medial PFC and parietal regions. Not only is cortisol implicated as a primary and interactive driver of activation in fMRI, but it may also selectively interfere with adaptive recruitment of stress- and regulatory- circuitry in MD.
Supported By: Support for this work was provided by the MH 091811 (SAL), MH 101487 (SAL), National Alliance for Research in Schizophrenia and Depression Award (SAL), and MH108258-01 (ATP).
Keywords: Cortisol, fMRI, Depression, Connectivity

132. Effects of Cortisol on Hippocampal Subfields and Centromedial Amygdala Volumes in Healthy Subjects and Patients With Major Depressive Disorder

Nikolai Malykhin[1], Scott Travis[1], Arash Aghamohammadi Sereshki[1], Nicholas Coupland[1], Peter Silverstone[1], Kathleen Hegadoren[1], Yushan Huang[1], Esther Fujiwara[1], Peter Seres[1], and Rawle Carter[1]

[1]University of Alberta

Background: Overactivity of the hypothalamic-pituitary-adrenal (HPA) axis in major depressive disorder (MDD) is among the most consistently replicated biological findings in psychiatry. The main goal of the present study was to examine the relationship between cortisol concentrations over a day, memory performance, hippocampal (HC) subfields and cetromedial amygdala volumes in MDD patients and healthy controls.
Methods: 24 MDD patients with moderate or severe episodes were recruited, together with 23 healthy controls. Imaging was performed using a 4.7T scanner. Participants were administered the Wechsler Memory Scale. The salivary cortisol levels were measured over the course of one day.
Results: We found that cortisol awakening response to 8h (CAR-8h) was higher in MDD patients compared to controls (p=0.03) and in MDD patients it correlated negatively with left total Cornu Ammonis (CA)1-3 and left HC head volume. In controls mean cortisol levels were negatively associated with right total CA1-3, right HC head, and right total HC volume. In addition, in controls higher CAR-8h was related to worse performance on the immediate content memory. The volume of centromedial amygdala in MDD patients was increased with disease progression (p=0.002) and was positively associated with mean cortisol concentration (p=0.04), while in healthy subjects with CAR-8h (p=0.03).
Conclusions: These results provide the first in-vivo evidence of the negative associations between cortisol level, CA1-3 volume and memory performance in MDD patients and healthy controls. The volume of cetromedial amygdala in MDD patients may be linked to the dysregulation of the HPA axis in depression.
Supported By: Canadian Institutes of Health Research (CIHR) operating grant MOP111049
Keywords: Depression, Cortisol, Hippocampus, Amygdala, Memory

SYMPOSIUM
New Insights Into Precision Medicine and Target Engagement in Depression Treatments
12:30 p.m. - 2:30 p.m.
Chair: Martijn Arns

133. Accelerated Intermittent Theta Burst Stimulation Rapidly Attenuates Depressive Symptoms and Suicide Ideation in Major Depression: Insights From Brain Perfusion and Functional Connectivity

Chris Baeken[1], Romain Duprat[2], Guo-Rong Wu[3], and Rudi De Raedt[1]

[1]Ghent University, [2]University of Pennsylvania, [3]Southwest University, Chongqing

Background: Accelerated repetitive transcranial magnetic stimulation paradigms have been shown to result in fast decreases in depressive symptoms and suicidal ideation. However, the neural working mechanisms behind this prompt attenuation on mood and suicidal thoughts, also after having received placebo stimulation, remains to be determined.
Methods: We present our recent brain imaging findings of an accelerated intermittent theta burst stimulation (aiTBS) protocol in treatment-resistant depression (TRD) focusing on arterial spin labeling (ASL) and subgenual anterior cingulate cortical (sgACC) functional connectivity (FC). By using a cross-over within-subjects design, 50 TRD patients received 20 iTBS sessions applied to the left dorsolateral prefrontal cortex (5 daily sessions spread over 4 days).
Results: Beneficial clinical outcome by active aiTBS strengthened sgACC - medial orbitofrontal cortex FC patterns which were associated with a decrease in feelings of hopelessness. Sham aiTBS specifically attenuated frontopolar perfusion in relation to reductions in suicidal ideation.
Conclusions: Our observations suggest possible neurobiological mechanisms why accelerated rTMS paradigms in depressed patients may result in prompt decreases in negative thinking.
Supported By: The Ghent University Multidisciplinary Research Partnership “The integrative neuroscience of behavioural control”.
Keywords: Major Depressive Disorder (MDD), rTMS, Resting State Functional Connectivity, Arterial Spin Labeling, Suicide

134. Optimizing TMS Treatment for Depression Using Cardiac Response With Neuro-Cardiac-Guided-TMS (NCG TMS)

Tabitha Iseger[1], Frank Padberg[2], J. Leon Kenemans[3], and Martijn Arns[4]

[1]Research Institute Brainclinics, Utrecht University, [2]Ludwig-Maximilian University, [3]Utrecht University, [4]Research Institute Brainclinics

Background: The efficacy of repetitive-Transcranial-Magnetic-Stimulation (rTMS), targeted at the Dorsolateral-Prefrontal-Cortex (DLPFC), to treat depression, has been well established. However, most studies haven't employed individualized methods. One way to individualize treatment is target engagement, by employing a functional outcome measure to verify localization. Given that DLPFC-TMS exerts its clinical benefit through connectivity with the subgenual-Anterior-Cingulate-Cortex (sgACC), we aimed to develop a method based on the role of the sgACC in autonomic regulation, particularly heart rate control. It has been demonstrated that stimulation of the sgACC and the DLPFC leads to heart rate decelerations, suggesting heart rate might serve as functional outcome measure.
Methods: 10Hz TMS (one train, 3 trials, 5 sec. 100% motor threshold, fig.8 coil) was applied to F3/FC3/C3, F4/FC4/C4 (10-20 system) in 10 subjects to investigate the location that most consistently resulted in heart rate deceleration. ECG was recorded simultaneously and converted to RR-intervals. The RR-respiratory troughs were scored and quantified to establish heart rate changes.
Results: F3 and F4 stimulation resulted in the largest heart rate deceleration, in line with studies suggesting these are optimal 10-20 sites to target the DLPFC (F3-C3:$p<0.009$; FC3-C3:$p<0.032$; F4-C4:$p<0.032$). However, 20% (left hemisphere) and 40% (right) of the subjects exhibited maximum heart rate deceleration at FC3 or FC4, indicating individual optima. For nobody this was C3 or C4, as expected.
Conclusions: This method, Neuro-Cardiac-Guided-TMS (NCG-TMS), may serve as target-engagement method for localizing the optimal TMS target treating depression. Furthermore, NCG-TMS test-retest reliability, dose- and treatment response (TMS non-responders retreated at their NCG-TMS individualized location), will be presented.
Keywords: Depression, TMS, DLPFC, Target Engagement, Heart Rate

135. Ketamine Treatment in Major Depression: Predictive Power of Heart Rate

Sebastian Olbrich[1], Torsten Meyer[1], Erich Seifritz[1], Tomas Palenicek[2], and Martin Brunowsky[2]

[1]University Zurich, [2]Prague Psychiatric Center & National Institute of Mental Health

Background: Ketamine has been shown to be effective in the treatment of therapy resistant episodes of major depressive disorder (MDD). Although some studies have evaluated possible clinical and anamnestic predictors of outcome following ketamine infusion there is a lack of objective biological markers. Therefore, this study aimed to analyze the predictive power of heart rate (HR) and heart rate variability (HRV) for ketamine treatment in major depressive disorder.
Methods: In 47 patients, electrocardiogram (ECG) was recorded and HR and HRV measures were assessed before and during a 10 minute ketamine infusion (0.5mg/kg) as well as 10 and 24 hours afterwards. Changes of depressive symptoms were assessed using the Hamilton Depression Rating scale, response was defined as a 33% reduction after 24 hours. A linear mixed model was used to analyze the discriminative and predictive power of HR and HRV measures.
Results: Ketamine infusion increased HR and HRV power during and after infusion with a return to baseline after 24 hours. Responders to ketamine showed a significantly higher HR ($F=10.86$, $df=147.65$, $p=.001$) with significant effects for covariates sex and age during the whole course of investigation, including the baseline condition in post-hoc testing with medium effect sizes (Cohen`s $d=0.47$-0.67). Also, HRV power discriminated between responders and non-responders ($F=6.65$, $df=133.30$, $p=0.011$), while normalized low/high frequency power did not.
Conclusions: HR and HRV power measures differed for responders and non-responders to ketamine infusion in MDD. Notably also the baseline parameters obtained before the infusion discriminated treatment outcome, suggesting HR and HRV as possible clinical useful predictive biomarkers.
Keywords: Major Depressive Disorder (MDD), Ketamine, Heart Rate, Treatment Prediction, Biomarker

136. Temporal Development of Depression Biomarkers From the iSPOT-D Study: State or Trait

Nikita van der Vinne[1], Martijn Arns[2], Michel van Putten[3], and Madelon Vollebregt[2]

[1]Research Institute Brainclinics, University of Twente, [2]Research Institute Brainclinics,, [3]University of Twente, Medisch Spectrum Twente

Background: In the quest for improving treatment prediction in depression, several promising prognostic baseline biomarkers for escitalopram, venlafaxine and sertraline have been identified, including frontal alpha asymmetry (FAA) and paroxysmal activity. As confirmed in our recent meta-analysis, FAA is not different between patients with and without depression, and hence it is hypothesized that FAA has state-independent characteristics. Differences in medication response in patients with paroxysmal EEG activity suggest a possible anticonvulsant property of sertraline relative to other antidepressants.
Methods: EEG data from 1008 MDD patients from the iSPOT-D trial at baseline and after 8 weeks of treatment (ITT sample=453), were quantitatively analyzed to calculate FAA (electrode (F4-F3)/(F4+F3)), and qualitatively screened by a blinded neurologist for paroxysmal activity.
Results: FAA at follow-up did not significantly differ from baseline measurements (n=453). With respect to paroxysmal activity, it was significantly more likely to find treatment

responders in the sertraline group compared to other prescribed antidepressants, if the EEG was deemed normalized at follow-up (odd's ratio=5.2, p=0.019, n=39). This likelihood was non-significant for subjects with unchanged paroxysmal EEGs (odd's ratio=2.8, p=0.325, n=18).
Conclusions: The trait-like, prognostic properties of FAA, implicate that FAA is more reflective of a trait rather than state. Patients with paroxysmal activity were more likely to respond to sertraline, but also patients that exhibited a normalized EEG from pre- to post-treatment were more likely to be a responder to treatment. These data suggest that sertraline's clinical effects are mediated by anticonvulsant properties where the normalized EEG can be considered a measure for target engagement.
Keywords: Depression, EEG, Frontal Alpha Asymmetry, Paroxysmal Activity, Biomarkers

SYMPOSIUM
Cross-Species Approaches to Elucidating In-Depth Neural Mechanisms, Biomarkers and Targets for Novel Neuromodulation Interventions in Mood Disorders and OCD

3:00 p.m. - 5:00 p.m.
Chair: Mary Phillips

137. Location of Anterior Cingulate and Ventrolateral Prefrontal Cortical Hubs: Integration Between Emotional and Cognitive Functions

Wei Tang[1], Anastasia Yendiki[1], Saad Jbabdi[2], and **Suzanne Haber**[3]

[1]Harvard Medical School, [2]Oxford University, [3]University of Rochester

Background: The anterior cingulate cortex (dACC) and ventromedial prefrontal cortex vmPFC are at the cross roads between emotional processing and cognitive function. Recent functional and structural MRI studies in humans have located 'hubs', areas that have unusually high connectivity with diverse brain areas. These regions are important for integrating and distributing information (Neuron, 79, 2013). Our goal was to anatomically identify dACC and vlPFC hub regions that may serve to integrate emotional processing and cognitive function. Guided by anatomic findings in monkeys, we identified hub locations in the dACC and vlPFC and their pathways using functional and structural MRI in humans.
Methods: Using stereology, we quantified the strength of inputs to the ACC and vlPFC following tracer injections into monkeys and charted their pathways. Using diffusion MRI in NHP and humans and functional MRI in humans we located the pathways and hubs in both species compared to the anatomic studies.
Results: The dACC hub received inputs from vlPFC orbital, and dorsal PFC, frontal eye fields and the amygdala. The vlPFC hub also received diverse multiple cortical areas. Fibers from these areas occupied ventromedial and ventrolateral positions respectively in the internal capsule. Using rsMRI and dMRI, we were able to demonstrate both the hubs and their fibers in the human brain.
Conclusions: The diversity of inputs to the dACC and vlPFC suggests there are key regions uniquely positioned for integrating emotional processing and cognition. These areas or their fibers are potential stimulation targets for psychiatric disorders, including mood disorders and OCD.
Supported By: MH045573. MH106435
Keywords: Obsessive Compulsive Disorder (OCD), Mood Disorders, Resting State fMRI, Diffusion MRI, Neuroanatomical Comparison

138. Biomarkers of Reward and Avoidance Neural Circuitry Abnormalities in Mood Disorders and OCD: Toward New Neural Targets for Neuromodulation Interventions

Mary Phillips[1], Henry Chase[2], Michele Bertocci[1], Amelia Versace[1], Simona Graur[2], Lisa Bonar[1], Richelle Stiffler[1], and Suzanne Haber[3]

[1]University of Pittsburgh, [2]University of Pittsburgh School of Medicine, [3]University of Rochester

Background: Abnormally elevated left ventrolateral prefrontal cortical (vlPFC)-ventral striatal (VS) activity during uncertain reward and outcome expectancy characterizes Bipolar Disorder (BD) and high impulsive sensation seeking. Persistent avoidance and abnormal orbitofrontal cortex (OFC) activity during avoidance acquisition characterize OCD. We are determining if these neural biomarkers are targets for neuromodulation for BD and OCD.
Methods: In ongoing studies: 1. euthymic adults with BD type I and healthy adults perform an fMRI reward task twice: during left vlPFC and left somatosensory cortex (SS) cathodal (inhibitory) transcranial direct current stimulation (tDCS); 2. adults with OCD and healthy adults undergo diffusion imaging and perform an fMRI task assessing persistent avoidance.
Results: To uncertain outcome expectancy, 13 BD adults showed greater left vlPFC activity than 13 healthy adults (p=0.17, trend) and left VS (p=0.029) to both tDCS conditions; BD, but not healthy, adults showed greater left amygdala activity during left vlPFC versus left SS tDCS (p=0.072). 28 OCD adults had lower fractional anisotropy in anterior-middle segments of the left cingulum bundle than 25 healthy adults ($p<0.05$, corrected). 22 OCD versus 22 healthy adults showed reduced OFC activity during avoidance acquisition ($p<0.005$,$k>20$ voxels).
Conclusions: In BD, left vlPFC cathodal tDCS may disinhibit the left amygdala (reducing amygdala inhibition by left vlPFC), thereby inhibiting dopaminergic inputs to VS via ventral striatum and pallidum, and is a promising neuromodulation intervention. Aberrant white matter in cingulum segments connecting anterior cingulate cortex and OFC, and reduced avoidance acquisition-related OFC activity, may predispose to persistent avoidance, and are potential targets for neuromodulation in OCD.
Supported By: R01 MH100041; P50 MH106435; R21 MH108421
Keywords: Bipolar Disorder, OCD, Biomarkers, Reward, Neuromodulation

139. Orbital-Cingulate Projections Modulating Persistent Avoidance in a Rodent Model of Compulsive Behavior

Freddyson Martinez-Rivera[1] and **Gregory Quirk**[1]

[1]University of Puerto Rico

Background: Compulsive behaviors of OCD often reflect persistent avoidance of perceived threats, despite competition with goal-directed behaviors. In a rodent model of persistent avoidance, we have observed increased activity in the rostral prelimbic cortex (rPL) (Bravo-Rivera et al, 2015), a homologue of human dorsal anterior cingulate cortex (dACC) (Heilbronner et al., 2016) that projects to ventral striatum (VS) to drive avoidance. Here we used optogenetics to investigate the role of the lateral orbital/anterior insula cortex (LO/AI), which project to both rPL and VS.
Methods: In response to a tone that signals a footshock, rats were trained across 8d to stop pressing for food and step onto a protective platform. They then receive 4 days of extinction training with a Plexiglas barrier blocking the platform, followed by a test session with the barrier removed. Rats were infused with AAV-CaMKIIa-eNpHR3-eYFP (Halo) or eYFP-only in LO/AI, and illuminated with yellow laser to silence LO/AI projections to either rPL or VS.
Results: cFos expression in rPL neurons was elevated in rats showing persistent avoidance at test. Photo-inhibiting projections from LO/AI to rPL increased persistent avoidance at test (eYFP, n=9: 17%; Halo, n=7: 54%, p=0.02), whereas photo-inhibiting LO/AI projections to VS had no effect.
Conclusions: Our findings suggest that persistent avoidance is induced by a failure of orbital/insular inputs to inhibit rPL activity. rPL appears to be a key hub because direct projections from LO/AI to VS are not involved. LO/AI may be homologous to human ventrolateral prefrontal cortex (vlPFC), which appears to be underactive in OCD.
Supported By: P50-MH106435, R37-MH058883
Keywords: Amygdala, Fear Extinction, Ventrolateral Prefrontal Cortex, Orbital Frontal Cortex, Prelimbic Cortex

140. Effects of Cathodal tDCS Over Pre-SMA on Brain Functional Connectivity in OCD

Benjamin Greenberg[1], Nicole McLaughlin[1], Jennifer Barredo[2], Brittney Blanchette[1], Steven Rasmussen[3], Noah Philip[2], and Linda Carpenter[1]

[1]Butler Hospital, [2]Providence VA Medical Center, [3]Brown Medical School

Background: Evidence suggests transcranial electrical or magnetic stimulation intended to reduce cortical excitability delivered over the pre-supplementary motor area (pSMA) might alter brain function and potentially symptomatology in individuals with obsessive-compulsive disorder (OCD). Our ongoing work tests effects of one such method, repeated cathodal transcranial DC stimulation (tDCS) over pSMA on brain circuitry.
Methods: OCD participants underwent 3T MRI for resting state functional connectivity (RSFC) before and after unmasked tDCS over pSMA for 10+ sessions. Stimulation was patterned on Reinhart and Woodson (J. Neuroscience, 2014), who found that cathodal tDCS suppressed error-related negativity thought to be generated by pSMA and underlying dorsal anterior cingulate cortex (dACC). We used a 5x5cm cathode over pSMA, a 5x7cm anode on the right cheek, and a current of 1.5mA delivered by a neuroConn stimulator for 20 minutes/session. We examined pSMA (MNI -3, 18, 57) RSFC across treatment using seed-to-voxel comparisons of baseline vs. post-tDCS RSFC. Given the small initial sample (N=9), statistical maps were leniently thresholded for signal detection (voxel p-uncorrected< 0.01, cluster p-uncorrected< 0.05).
Results: We found RSFC between pSMA and left ventrolateral prefrontal cortex (-48 34 -10) increased after tDCS, whereas connectivity between pSMA and left dACC (-4 2 30) and right insula (42 4 -2) decreased (maximum Z=5.42). Mean changes in clinical and functional ratings were not significant.
Conclusions: The data suggest this tDCS regimen might engage cognitive control and emotion processing regions possibly regulating a “core” OCD circuitry. Relationships between individual RSFC and clinical changes will be tested in the larger final sample.
Supported By: NIMH P50 MH106435; VA ORD RR&D N9228-C
Keywords: OCD, Transcranial Direct Current Stimulation (tDCS), Resting State Functional Connectivity, Pre-Supplementary Motor Area, Ventrolateral Prefrontal Cortex

SYMPOSIUM
Therapeutic Strategies to Enhance Emotion Regulation: Models Derived From Neuroscience
3:00 p.m. - 5:00 p.m.
Chair: Harold Koenigsberg

141. Enhancing Emotion Regulation in Borderline Personality Disorder Patients Through Longitudinal Reappraisal Training: Evidence From Self-Reported Negative Affect and fMRI

Harold Koenigsberg[1], Bryan Denny[2], Jin Fan[1], Halyley Galitzer[1], Samuel Fels[1], Liza Rimsky[3], Antonia McMaster[4], Antonia New[1], Mercedes Perez-Rodriguez[1], Erin Hazlett[1], Daniel Rosell[1], and Margaret McClure[5]

[1]Icahn School of Medicine at Mount Sinai, [2]Rice University, [3]New York University, [4]City University of New York, [5]Fairfield University

Background: Borderline personality disorder (BPD) is the prototypical disorder of emotion dysregulation. We have shown previously that when BPD patients attempt the highly adaptive emotion regulatory strategy of cognitive reappraisal, they do not engage brain regions known to participate in healthy individuals. In this study, we assessed whether BPD patients could be trained to improve cognitive reappraisal and normalize neural activity.
Methods: At each of six sessions, BPD and healthy control (HC) participants were shown negative social emotional

images and instructed to employ cognitive reappraisal by distancing. On days 2 through 5, subjects were trained in distancing by guided instruction supplemented by repeated practice. fMRI data were acquired at sessions 1, 5, and 6, 2-weeks later. The present analyses reflect data from a preliminary sample of 14 BPD's and 16 HC's (sessions 1-5) and 10 BPD's and 13 HC's who also completed session 6.
Results: BPD's showed significantly reduced negative emotion self-reports during reappraisal-by-distancing over the course of the training period ($p<.009$) and this was maintained over the follow-up period ($p<.004$) (session 1 to 6). Further, with training, BPD's, who had not decreased amygdala activity on day 1, were able to do so when reappraising on day 5 ($p<.05$). This attenuation was preserved at follow-up session two weeks later. With training, BPD patients also increased reappraisal activity in ventrolateral prefrontal cortex, a region shown to be engaged during reappraisal in HC's.
Conclusions: These data represent the first evidence that longitudinal training can increase reappraisal success and normalize reappraisal neural activity in any patient population.
Supported By: NIMH R01 MH077813
Keywords: Cognitive Reappraisal, Affective Instability, Emotion Regulation, Borderline Personality Disorder

142. Enhancing Emotion Regulation Through Longitudinal Training in Cognitive Reappraisal: A Translational Social Cognitive Neuroscience Approach

Bryan Denny[1]

[1]Rice University

Background: Cognitive reappraisal involves reframing an emotional stimulus in a way that changes its emotional impact. Reappraisal has been shown to be effective in single sessions. Little is known, however, about whether one can improve over time in implementing reappraisal, and how reappraisal responses endure in both healthy and stressed populations.
Methods: In two studies, reappraisal was operationalized using two different tactics: distancing (i.e. thinking about an emotional stimulus as an impartial observer) and reinterpretation (i.e. imagining a better outcome). The first study examined whether healthy adults could improve in their ability to use reappraisal to down-regulate negative affect using either distancing or reinterpretation over the course of four experimental sessions over two weeks using an image-based reappraisal task. Three groups were recruited: distancing ($N=33$), reinterpretation ($N=33$), and a no-regulation control group ($N=33$). In the second, on-going study, recently bereaved spouses ($N=9$) underwent five sessions of distancing or reinterpretation training over two weeks, with longitudinal collection of grief rumination self-reports and neural activity via fMRI.
Results: In the first study, reappraisal-by-distancing participants showed significant longitudinal reductions in self-reported negative affect ($p<0.01$) that were not attributable to habituation and further uniquely showed reductions in perceived stress in daily life ($p<0.03$). In the second study, preliminary analyses have revealed that, in contrast to reinterpretation training, distancing training in recently bereaved spouses is associated with reduction in grief rumination ($p<0.02$).
Conclusions: These studies show that reappraisal, particularly reappraisal-by-distancing, is trainable and adaptive and suggest future translational investigations of reappraisal training in affectively-disordered populations.
Supported By: R01MH076137; Rice University Faculty Initiatives Fund
Keywords: Emotion Regulation, Cognitive Reappraisal, Longitudinal, Perceived Stress, Bereavement

143. Amygdala Emotional Regulation Training With Real-Time fMRI Neurofeedback and Concurrent EEG Recordings

Jerzy Bodurka[1]

[1]Laureate Institute for Brain Research

Background: Asymmetrical frontal EEG and aberrant BOLD prefrontal cortex (PFC) and amygdala responses indicate emotion and approach motivation deficits in MDD and PTSD. Real-time fMRI neurofeedback (rtfMRI-nf) with EEG offers a non-invasive brain neuromodulation approach to normalize amygdala, PFC responses.
Methods: rtfMRI-nf with EEG to upregulate left amygdala (LA, experimental group EG) BOLD activity during happy memory recall. In controls, nf was from a region not involved in emotions. Connectivity analysis identified regions engaged during LA training - structural vector autoregression (SVAR) analysis elucidated interactions. Frontal EEG asymmetry (FEA, right vs left) in the upper-alpha band and BOLD correlations were studied. The linear increase in the target level for LA upregulation across four nf runs introduced trends in fMRI connectivity and in EEG coherence, characterized with EEG-coherence slope (ECS).
Results: Only in EG, rtfMRI-nf of LA resulted in BOLD signal increase and in significantly decreased depression in MDD (HDRS,$n=14$,$p<.05$) and decreased PTSD symptoms in veterans (CAPS,$n=15$,$p<.0024$). In MDD, SVAR analysis showed left rostral anterior cingulate (rACC) and left prefrontal DLPFC/DMPFC engagement with LA. EEG during nf-training showed correlations between LA BOLD activity and FEA ($r=.41$,$p=.0001$). Left fronto-temporal ECS-enhancements during nf-training positively associated with HDRS (MDD,$r=.64$,$p=.017$) and CAPS (PTSD,$r=.74$,$p=.0006$). Successful rtfMRI-nf LA training, normalized FEA, and increased ECS associated with improved emotion and motivation.
Conclusions: rtfMRI-nf LA training reduces MDD, PTSD symptoms, enhances left fronto-temporal EEG coherence improving emotions and approach motivation. rtfMRI-nf with EEG offers a targeted approach to modulate circuits and research novel portable psychiatric interventions.
Supported By: W81XWH-12-1-0697 grant from the U.S. Department of Defense
Keywords: Concurrent EEG/fMRI, Neurofeedback, Amygdala, Emotion Regulation, MDD, PTSD

144. Brief Mindfulness Intervention Improves Emotion Regulation in Healthy and Patient Populations

Yi-Yuan Tang[1]

[1]Texas Tech University

Background: One form of mindfulness intervention - Integrative Body-Mind Training (IBMT) improves self-control ability through strengthening brain activity and connectivity of anterior cingulate cortex (ACC), prefrontal cortex (PFC) and striatum. Depression often shows deficits in self-control of attention, emotion. However, whether a brief mindfulness intervention reduces affective state dysregulation and symptoms remains unclear. This pilot study aims to examine the efficacy of IBMT in college students with first episode depression and its brain mechanism.
Methods: Thirty-three first episode depression (DSM-IV depression diagnosis) and 33 matched healthy college students without any treatment history participated this study. Studies indicate that IBMT improves self-control through interaction between the central and autonomic nervous systems. Subjects received 10 hours of IBMT in total, in twenty 30 min-sessions over 4 weeks. Before and after intervention, subjects completed the Attention Network Test and Profile of Mood States to assess changes in self-control. Brain measurement of cerebral blood flow (CBF) was used to detect brain changes using GE 3-head SPECT scanner.
Results: Before intervention, compared to healthy controls, the depression group showed deficits in executive attention ($p=0.004$) and greater anger, depression, fatigue, anxiety, and confusion; CBF showed global reductions especially at ACC and adjacent PFC, insula and striatum, associated with self-control and reward (all $p<0.05$). After intervention, all attention and mood indexes and the CBF of the above regions showed significant increases (all $p<0.05$).
Conclusions: Brief mindfulness intervention has the potential to help mood disorders through improved regulation of self-control and reward networks in the brain.
Supported By: John Templeton Foundation
Keywords: Mindfulness Intervention, Emotion Regulation, Self-Control Networks, Depression

SYMPOSIUM
Validation of Brain-Based Biotypes for Classification of Individuals on the Psychosis Spectrum: Findings From the B-SNIP Consortium

3:00 p.m. - 5:00 p.m.
Chair: Synthia Guimond
Co-Chair: Sinead Kelly

145. Diagnosis and Biotype Comparisons Across the Psychosis Spectrum: Investigating Amygdala-Hippocampal Differences From the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study

Synthia Guimond[1], Sinead Kelly[1], Luke Mike[2], M. Mallar Chakravarty[3], John Sweeney[4], Godfrey Pearlson[5], Brett A. Clementz[6], Carol Tamminga[4], and Matcheri Keshavan[1]

[1]Harvard Medical School - Beth Israel Deaconess Medical Center, [2]Beth Israel Medical Center, [3]Douglas Mental Health University Institute, McGill University, [4]UT Southwestern Medical Center, [5]Hartford Hospital, Yale University School of Medicine, [6]University of Georgia

Background: Identifying biomarkers that differentiate patients across the psychosis spectrum has been challenging. In response to this challenge, the B-SNIP consortium has identified brain-based Biotypes independent of clinical phenomenology to classify patients. Here we used amygdala-hippocampal volume and shape data as external validators for comparing both, Biotypes and clinical categorization across the psychosis spectrum.
Methods: Individuals with schizophrenia (SZ, n=186), schizoaffective disorder (SZA, n=116), and psychotic bipolar disorder (PBD, n=173), as well as healthy controls (HC, n=315) across six sites were included in the study. Amygdala–hippocampal volumes and surface area metrics were extracted from the T1-weighted images with the MAGeT-Brain algorithm. General linear models tested for main effect of Biotype and diagnosis, while covarying for confounds (age, sex, handedness, race, intracranial volume, and site).
Results: SZ and SZA showed smaller amygdala-hippocampal volume compared to HC ($d=0.19$-0.33;$p<.05$). Abnormal shape of these structures was also present in all diagnostic groups ($p<.05$). Biotype 1 showed smaller amygdala-hippocampal volume than healthy controls ($d=0.48$-0.58;$p<.05$) and other Biotypes ($d=0.31$-0.54;$p<.05$). No significant volume differences were observed between Biotypes 2, 3 and HC. Biotype 3 showed subtle hippocampal shape differences compared to Biotype 2 and HC ($p<.05$).
Conclusions: While diagnosis comparison results are consistent with previous findings, larger effects were observed when using Biotype classification. Patients in Biotype 1 not only have significant amygdala and hippocampus volume and shape differences compared to HC, but also compared to other Biotypes. Grouping patients by Biotype, given that imaging data were not used in construction of these categories, may be more biologically valid.
Supported By: MH 78113
Keywords: Psychosis Phenotype, Amygdala, Hippocampus, Biotypes, Biomarkers

146. Diagnosis and Biotype Comparisons Across the Psychosis Spectrum: Investigating White Matter Microstructural Differences From the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study Using Free-Water Imaging

Sinead Kelly[1], Synthia Guimond[1], John Sweeney[2], Godfrey Pearlson[3], Brett Clementz[4], Carol Tamminga[2], Martha Shenton[5], Ofer Pasternak[6], and Matcheri Keshavan[7]

[1]Harvard Medical School - Beth Israel Deaconess Medical Centre, [2]UT Southwestern Medical Center, [3]Yale University, School of Medicine, [4]University of Georgia, [5]Brigham and Women's Hospital, Harvard Medical School, VA Boston Healthcare System, [6]Brigham and Women's Hospital, Harvard Medical School, [7]Beth Israel Deaconess Medical Center

Background: In order to classify individuals across the psychosis spectrum, the B-SNIP consortium identified three neurobiologically distinct biotypes, independent of clinical phenomenology. To externally validate the Biotype model, we used free-water fractional volume (FW) and free-water corrected

fractional anisotropy (FAT) to compare white matter differences across brain-based biotypes and clinical categorization.
Methods: Diffusion tensor imaging (DTI) data from 36 individuals with schizophrenia (SZ), 15 with schizoaffective disorder (SAD), 17 with psychotic bipolar disorder (PBD), and 30 healthy controls (HC) from the Baltimore site in the B-SNIP-1 consortium were included. FW and FAT images were analysed using ENIGMA TBSS protocols and the corpus callosum (CC), body (BCC), splenium (SCC) and genu (GCC) regions of interest (ROIs) were extracted. General linear models were applied to test for main effect of Biotype and diagnosis, covarying for age, sex and race.
Results: SAD showed lower FAT in CC (d=0.6;p=.04) and BCC (d=.55;p=.036) compared to HC. Using Biotype classification, Biotype 1 showed lower FAT than healthy controls for the CC (d=.91;p=.003) and lower FAT compared to Biotype 3 for the BCC (d=.56;p=.04). Although a significant Biotype difference was observed for FW of the CC (F=3.0;p=.03), pairwise comparisons were not significant.
Conclusions: While significant diagnosis comparisons were observed between SAD and HC, larger effects were observed when using Biotype classification. Patients in Biotype 1 not only have significant FAT differences in the CC compared to HC, but also compared to Biotype 3. Therefore, grouping patients by Biotype may be a more biologically valid approach.
Supported By: MH 78113 and MH 96942

The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) is a research study to understand the genetic basis and brain changes in those with schizophrenia/schizoaffective and bipolar disorder
Keywords: Schizophrenia, Psychosis Phenotype, Biotypes, Diffusion Tensor Imaging (DTI), White Matter

147. Resting State Connectivity in Traditional and Biologically Derived B-SNIP Psychosis Subtypes

Shashwath Meda[1], Brett Clementz[2], John Sweeney[3], Matcheri Keshavan[4], Carol Tamminga[3], Elena I. Ivleva[3], and Godfrey Pearlson[5]

[1]Hartford Healthcare, [2]University of Georgia, [3]UT Southwestern Medical Center, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, [5]Olin Neuropsychiatry Research Center

Background: Traditional psychiatric diagnostic approaches have long relied on symptomatology, which has prompted a recent shift in utilizing more objective, biological based classifications. The current aim was to contrast intrinsic resting state fMRI (rs-fMRI) connectivity measures in psychotic patients using conventional DSM-IV diagnoses versus a more objectively derived criteria based on cognitive/neurophysiological data (B-SNIP-derived Biotypes).
Methods: The study included 258 healthy controls (HC), 518 probands (schizophrenia (SZ), schizoaffective disorder (SAD), psychotic bipolar disorder (PBP) and 349 relatives of probands (R). Probands and relatives were also segregated into Biotype groups (B1-B3, B1R-B3R using a method reported previously). Resting networks were derived using independent component analysis (ICA). Average coefficient measures were extracted across voxels that differed in probands (pooled) vs controls. Post-hoc t-tests were performed on summary measures across DSM diagnoses and Biotypes.
Results: Voxel-wise tests between probands and controls revealed nine abnormal networks ($p<0.05$ FWE). Post-hoc analysis on average connectivity coefficients indicated all networks had lower connectivity in at least one DSM and/or Biotype proband group ($p<0.05$ FDR). However, across DSM groups, no between-proband differences were detected, while 4/9 networks showed at least one significant post-hoc difference among Biotype probands. Follow-up mixed effect analyses revealed significant biotype/DSM interactions in a subset of the above networks. Reduced connectivity was noted in SZ-R in two networks and PBP-R in one network. Similarly, Biotype relatives showed similar deficits in one network.
Conclusions: For phenotype studied here, Biotypes seem to be more sensitive in capturing differences among psychosis probands over conventional DSM diagnoses, thus confirming their validity.
Supported By: MH077851, MH078113, MH077945, MH077852, MH077862
Keywords: Independent Components Analysis, Network, Biotypes, Classification, Connectivity

148. Auditory and Visual EEG Validators of Psychosis Biotypes, Findings From Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium

David Parker[1], Rebekah Trotti[1], Jennifer E. McDowell[1], Sarah Keedy[2], John Sweeney[3], Elliot Gershon[2], Godfrey Pearlson[4], Matcheri Keshavan[5], Carol Tamminga[6], and Brett Clementz[1]

[1]University of Georgia, [2]University of Chicago, [3]University of Cincinnati, [4]Yale University School of Medicine, [5]Harvard University, [6]UT Southwestern Medical Center

Background: Multiple auditory and visual electrophysiology (EEG) measures have shown large deviations in evoked responses in psychotic subgroups. This has raised the possibility that they are distinct biomarkers and could be used as validators of psychosis Biotypes identified by the B-SNIP consortium.
Methods: 305 individuals (HC=82, SZ=66, SAD=64, BD-WP=59, BD-NP=34) completed 5 EEG measures (Oddball: OB, Paired Stimuli: PS, Auditory Steady-State: aSSR, Visual Steady-State: ssVEP, and Emotional-IAPS), the BACS, and pro-/anti-saccade tasks. Using the variables that were most important in the B-SNIP-1 Biotype classification (OB, PS, BACS, Pro-/Anti-Saccades), the 3 Biotypes were approximated using psychosis subjects from an independent BSNIP-2 sample (N=189; B1=40, B2=63, B3=86). Twenty-seven variables from 3 novel EEG tasks (aSSR, ssVEP, and IAPs) that significantly differentiated HC from psychosis subgroups were used to compare differences in neurophysiological profiles and separation of Biotype and DSM subgroupings with a multivariate canonical discriminant analysis.
Results: Two components were identified for both DSM ($p<.001$; $p=.0013$) and Biotypes ($p<.001$; $p=.023$). DSM and Biotype components revealed distinct neural profiles. Biotypes

had reduced variability, showed a greater separation from HC and BDNP, and had greater separation between psychosis subgroups than DSM subgroups. 2-Dimension distance effect sizes for DSM= SZ vs SAD: 0.14; SZ vs BDP: 0.64; SAD vs BDP: 0.54. Biotypes= B1 vs B2: 0.83; B1 vs B3: 0.49; B2 vs B3: 0.71.
Conclusions: These validators provide evidence that the psychosis Biotypes identified by the B-SNIP consortium have significant promise in delineating biologically valid subgroups which could lead to novel drugs, treatment, and identification of genetic causes.
Supported By: NIMH Multiple RO1s Psychosis and Affective Research Domains and Intermediate Phenotypes (PARDIP) NIMH: Multiple RO1s Bipolar-Schizophrenia Network for Intermediate Phenotypes 2 (BSNIP-2); Franklin Foundation Neuroimaging Training Program
Keywords: Biomarkers, EEG, Multivariate Analysis, Auditory Processing, Visual Processing

SYMPOSIUM
Digital Phenotyping: Advances in Smartphone Sensing, Data Analytics, and Inferring Clinically-Relevant Information

3:00 p.m. - 5:00 p.m.
Chair: Jukka-Pekka Onnela
Co-Chair: Patrick Staples

149. Characterizing the Clinical Relevance of Digital Phenotyping Data Quality With Applications to a Cohort With Schizophrenia

Patrick Staples[1], John Torous[2], Ian Barnett[3], Luis Sandoval[4], **Matcheri Keshavan**[5], and Jukka Pekka Onnela[1]

[1]Harvard School of Public Health, [2]Beth Israel Deaconess Medical Center, [3]University of Pennsylvania Perelman School of Medicine, [4]Harvard Medical School, [5]Harvard University

Background: Digital phenotyping holds great potential for behavioral monitoring of patients. However, realizing the potential of digital phenotyping requires understanding of the smartphone as a scientific data collection tool.
Methods: We present a novel procedure for estimating data quality for phone sensor samples and model the relationship between data quality and future symptom-related survey responses in a cohort with schizophrenia (n=16; 3 months follow-up).
Results: Measures of empirical coverage of collected accelerometer and GPS data, as well as survey timing and survey completion metrics, are significantly associated with future survey scores for a variety of symptom domains ($p<0.05$; corrections for multiple testing required). We also find evidence that specific measures of data quality are indicative of domain-specific future survey outcomes.
Conclusions: These results suggest that for smartphone-based digital phenotyping, metadata is not independent of patient-reported survey scores, and is therefore potentially useful in predicting future clinical outcomes.

Supported By: NIH-NIMH
Keywords: Individual Patient Data, Data-driven Analytics, Schizophrenia, Predictive Analytics

150. Automated Longitudinal Latent Interval Estimation With Applications to Sleep

Jukka-Pekka Onnela[1], Matcheri Keshavan[2], **Patrick Staples**[1], Ian Barnett[1], and John Torous[2]

[1]Harvard TH Chan School of Public Health, [2]Beth Israel Deaconess Medical Center

Background: Adequate and regular sleep are required for longevity and mental health. Estimating sleep over time is difficult due to the paucity of unobtrusive longitudinal data related to sleep. Retrospective recall suffers from poor accuracy, even over short time scales. Sleep diaries are generally accurate measures of sleep duration, but are infeasible as passive measurements of sleep. Dedicated devices such as actigraphy watches and polysomnograms are also infeasible when not in a study setting. We propose a digital phenotyping approach, using arbitrary smartphone activity data to estimate sleep. Although smartphone ownership and usage continue to increase, accounting for the indirect relationship between smartphone activity and sleep status presents unique challenges, for which strong but potentially testable assumptions must be made.
Methods: We introduce an unsupervised, subject-specific, longitudinal, likelihood-based framework for estimating the latent daily onset of sleep and waking from arbitrary smartphone activity data and longitudinal covariates. We compare the empirical and theoretical bias and variance of parameter estimates via simulation and apply the method to several ongoing digital phenotyping studies.
Results: In a cohort of healthy students at Harvard College (n=19), the accuracy of our estimates of sleep match those of FDA-approved actigraphy devices by over 95% in median cases. In several clinical pilot studies (combined $n \sim 150$) we show that mean sleep and waking onset times are significantly related to clinical survey scores over time. (As p-values are estimated within patient, significance reports require adjustment for multiple testing.)
Conclusions: Estimating sleep from passive smartphone data is both accurate and amenable to statistical inference.
Supported By: NIH; NIMH; Other
Keywords: Sleep Duration, Binge Eating Disorder, Schizophrenia, Bipolar Disorder

151. Relapse Prediction in Schizophrenia through Digital Phenotyping

Ian Barnett[1], John Torous[2], Patrick Staples[3], Luis Sandoval[4], Matcheri Keshavan[5], and Jukka-Pekka Onnela[3]

[1]University of Pennsylvania Perelman School of Medicine, [2]Beth Israel Deaconess Medical Center, [3]Harvard TH Chan School of Public Health, [4]Harvard Medical School, [5]Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Among individuals diagnosed, hospitalized, and treated for schizophrenia, up to 40% of those discharged may relapse within one year even with appropriate treatment. Passively collected smartphone behavioral data present a scalable and at present underutilized opportunity to monitor patients in order to identify possible warning signs of relapse.
Methods: In a pilot study, 17 patients with schizophrenia in active treatment at a state mental health clinic in Boston used the Beiwe app on their personal smartphone for up to three months. By testing for changes in mobility patterns and social behavior over time as measured through smartphone use, we were able to identify statistically significant anomalies in patient behavior in the days prior to relapse.
Results: We found that the rate of behavioral anomalies detected in the two weeks prior to relapse was 71% higher than the rate of anomalies during other time periods.
Conclusions: Our pilot study findings show how passive smartphone data, data collected in the background during regular phone use without active input from the subjects, may provide a new and detailed view into patient behavior outside the clinic. Real-time detection of behavioral anomalies may signal the need for an intervention before an escalation of symptoms and relapse occur, therefore reducing patient suffering and reducing the cost of care.
Supported By: NIH/NIMH 1DP2MH103909; Harvard McLennan Dean's Challenge Program; Natalia Mental Health Foundation
Keywords: Personalized Medicine, Translational Research, Schizophrenia, Mobile Health Application, Relapse Prediction

152. Technology and Smartphone Ownership, Interest, and Engagement Among Those with Schizophrenia

John Torous[1]

[1]Harvard Medical School

Background: As interest in mobile mental health technologies continues to increase — it is important that the patient perspective also be kept in mind. Numerous pilot studies have confirmed both the feasibility, and some even the efficacy, or smartphone technologies for monitoring and assisting in the management of individuals with schizophrenia. Yet less is known about how those individuals with schizophrenia feel about the role of technology in their care and whether they are interested in using mobile devices to monitor their mental health in everyday life outside of clinical studies.
Methods: An online survey of individuals eighteen years or older with schizophrenia or schizoaffective disorders regarding their use and attitudes towards technology. Respondents were recruited from those involved with the National Alliance of Mental Illness (NAMI).
Results: A total of 457 individuals with schizophrenia or schizoaffective disorders completed the survey. The majority (90%) of people living with schizophrenia have access to more than one device. Most commonly, people living with schizophrenia say they have access to a personal computer (89%) followed by a Smartphone (54%) and landline phone (52%). Of those who have access to connected device, individuals living with schizophrenia spent, on average, 5 hours per day on a personal computer and 4 hours on a smartphone.
Conclusions: Results of the survey suggest that individual with schizophrenia or schizoaffective disorder commonly use and own connected technologies like smartphones. Many find devices useful in self-managing symptoms of schizophrenia — although in some case may be overusing and at risk for Internet addiction disorder.
Supported By: NARSAD Young Investigator Award. Natalia Mental Health Foundation. Harvard Medical School Dupont Warren Fellowship.
Keywords: Deep Learning Technology, Online Game Addiction, Schizophrenia

SYMPOSIUM
Behavioral and Immune Causes and Consequences of Inflammation in Depression
3:00 p.m. - 5:00 p.m.
Chair: Manish Jha
Co-Chair: Madhukar Trivedi

153. Inflammation Effects on Motivation and Motor Activity: Dopamine as Mediator and Treatment Target

Andrew Miller[1], Ebrahim Haroon[2], and Jennifer Felger[2]

[1]Emory University School of Medicine, [2]Emory University

Background: Increased inflammation has been observed in many psychiatric disorders including major depression. Work by our group and others has demonstrated that inflammation has specific effects on basal ganglia regions that mediate inflammation-associated decreases in motivation and motor activity. These effects of inflammation appear to be related in part to the impact of inflammation on dopamine in key basal ganglia regions including the ventral striatum.
Methods: Studies using neuroimaging (PET and fMRI) and in vivo microdialysis have been conducted in humans and nonhuman primates administered the inflammatory cytokine interferon (IFN)-alpha along with studies using neuroimaging (fMRI) and anti-inflammatory (anti-cytokine) treatment of patients with major depression.
Results: IFN-alpha was associated with decreased activation of ventral striatum in motivational tasks ($n=28$, $p<0.01$) and increased reuptake and decreased release of dopamine in caudate and putamen ($n=12$ pre-post design all $p<0.01$). Impaired dopamine release in nonhuman primates was reversed by levodopa administered by reverse microdialysis and was correlated with decreased effort expenditure for reward. Studies in humans with depression indicate that increased inflammation was associated with decreased connectivity in reward circuits involving ventral striatum and ventromedial prefrontal cortex ($n=48$, $p<0.05$ corrected) that correlated with decreased motivation ($p=0.001$) and psychomotor speed ($p=0.015$). Anti-cytokine treatment ($n=60$) reduced symptoms of anhedonia and psychomotor retardation in patients with major depression and increased inflammation.
Conclusions: These data suggest that depressed patients with increased inflammation may preferentially respond to medications targeting dopamine pathways. Although data

from laboratory animals is in support of this possibility, future studies are needed to test this hypothesis in humans.
Supported By: R01MH087604, R01MH083746, R21MH0771172
Keywords: Inflammation, Motivation, Ventral Striatum, Dopamine, Brain Reward Circuit

154. Gender-Specific Association of IL-17 with Anhedonia in Depressed Outpatients: Findings From CO-MED Trial

Manish Jha[1], Andrew Miller[2], Abu Minhajuddin[3], and Madhukar Trivedi[3]

[1]UT Southwestern, [2]Emory University, [3]University of Texas Southwestern Medical Center

Background: Among individual depressive symptoms, anhedonia (loss of interest or pleasure) has been consistently shown to worsen with increased inflammatory markers in depressed patients. However, it is unclear whether gender differentially affects association of anhedonia with peripheral inflammatory markers, especially interleukin-17 (IL-17).
Methods: Levels of inflammatory biomarkers (IL-17, T-helper (Th) 1, Th2 and non-T cell markers) were measured with the Bioplex ProTM human cytokine 27-plex kit in Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants who provided plasma at baseline (n = 166). Anhedonia was measured with three items of the 30-item Inventory of Depressive Symptomatology clinician-rated version and depression severity was measured with Quick Inventory of Depression Severity. Separate general linear model with gender-by-inflammatory marker interaction and anhedonia and overall depression severity as dependent variable were used to test for differential association of anhedonia with inflammatory (IL-17, Th1, Th2, and non-T cell) markers based on gender. Subsequent analyses stratified by gender were conducted for those markers with a significant interaction.
Results: Based on gender, there was differential association of anhedonia with IL-17 (p=0.05) but not with Th1 (p=0.20), Th2 (p=0.74) and non-T cell (p=0.49) markers. Anhedonia severity increased with increase in IL-17 in males (r=0.42, p=0.0025) but not in females (r=0.09, p=0.34). There was no significant gender-specific difference in association of the inflammatory markers and overall depression severity.
Conclusions: Gender is an important biological factor which moderates association of IL-17 mediated immune response and anhedonia. Males but not females experience greater severity of anhedonia with higher levels of peripherally circulating IL-17.
Supported By: NIMH, The Hersh Foundation, The Jordan Harris Foundation
Keywords: Inflammation, Interleukin-17, Gender Differences, Anhedonia, Major Depressive Disorder (MDD)

155. Infectious Agents, Adaptive Immunity and Inflammation in Depression

Jonathan Savitz[1]

[1]Laureate Institute for Brain Research

Background: Dysregulation of both innate and adaptive immunity are associated with depression, leading to inflammation and immune suppression, respectively. Nevertheless, the etiological factors contributing to immune dysfunction remain unclear, limiting possibilities for intervention.
Methods: Here, we measured CRP (index of inflammation), measles serostatus (measure of maintenance of immunity to a vaccine, i.e. a heuristic index of adaptive immune function), Toxoplasma gondii (Toxo), and cytomegalovirus (CMV) serostatus in 179 subjects meeting DSM-IV-TR criteria for mood disorders (major depressive disorder and bipolar disorder) and 223 comparison controls (HC).
Results: There was no significant group difference in CRP. Nevertheless, within the mood disorder group, there was a positive correlation between CRP and anhedonic symptoms that trended significant (r=0.14, p=0.061) as well as a positive correlation between self-reported sleep disturbance and CRP (r=0.20, p=0.048). Logistic regression analyses showed that subjects with mood disorders were significantly less likely to test seropositive for measles than HC (adjusted OR=0.53, CI=0.31-0.88, p=0.015). In contrast, the mood disorder group was more likely than HC to test seropositive for Toxo (OR=2.09, CI=0.99-4.43, p=0.051) and CMV (OR=1.71, CI=1.13–2.49, p=0.011).
Conclusions: The following results should be interpreted within limitations of a cross-sectional design and a single time-point measure of CRP. First, the behavioral domains of reward-processing and sleep may be disproportionately affected by inflammation. Second, adaptive immunity is impaired in depression. Third, certain infections are more common in depression. Nevertheless, we could not establish a clear link between inflammation, adaptive immune dysfunction, and Toxo or CMV serostatus, indicating that these may be separate pathophysiological phenomena.
Supported By: NARSAD
NIGMS
Keywords: Inflammation, Infection, Depression, Toxoplasma Gondii, Sleep Disturbances

156. Inflammation Selectively Impairs Executive Function in Treatment-Resistant Depressed Outpatients: Findings From TREAD Study

Tracy Greer[1], Manish Jha[1], Bruce Grannemann[1], Abu Minhajuddin[1], and **Madhukar Trivedi**[1]

[1]University of Texas Southwestern Medical Center

Background: Depressed patients exhibit significant cognitive impairments, especially in domains of attention and executive function. While inflammation has gained recent attention in depression, its role in pathophysiology of impaired cognition remains unclear.
Methods: Treatment with Exercise Augmentation for Depression (TREAD) study participants (n=77) who provided serum and completed Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline were included in this report. Interferon gamma (IFN γ), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) were measured in serum using a multiplex MesoScale Discovery assay. Association of inflammatory markers with performance on CANTAB measures

assessing attention, visual memory, spatial planning, and spatial working memory were tested with separate multivariate analyses of variance after controlling for gender, age, education and body mass index. Correlation analyses described the relationship between individual inflammatory markers and cognitive tasks.
Results: Higher levels of IL-6 (F=3.61, p=0.03) and IFN γ (F=4.51, p=0.01) were associated with worse performance on attention tasks. Higher IL-6 levels were also associated with poorer performance on spatial planning tasks (F=8.90, p $<$0.0001). On the spatial planning tasks, higher IL-6 levels were associated with longer initial thinking time to plan a problem solution for trials requiring two [correlation coefficient (r)=0.28, p=0.04], three (r=0.42, p=0.0007), four (r=0.45, p=0.0002), and five (r=0.52, p$<$0.0001) moves. There was no association between CANTAB measures and IL-1β or TNF-α.
Conclusions: Depressed patients with higher IL-6 levels exhibit progressive worsening of performance on spatial planning task of increasing complexity. Targeting inflammation presents a promising avenue to improve cognition in depressed patients.
Supported By: NIMH R01-MH067692-01; NARSAD
Keywords: Neuroinflammation, Treatment Resistant Depression, Interleukin-6, Executive Function, Neurocognition

SYMPOSIUM
Genomics of PTSD: Large-Scale Consortia Efforts, First Robust Associations, and Moving Beyond

3:00 p.m. - 5:00 p.m.
Chair: Caroline Nievergelt

157. Large-Scale Genetic Characterization of PTSD: Addressing Heterogeneity Across Ancestry, Sex, and Trauma

Caroline Nievergelt[1], Adam Maihofer[1], Shareefa Dalvie[2], Laramie Duncan[3], Andrew Ratanatharathorn[4], Kerry Ressler[5], Israel Liberzon[6], and Karestan Koenen[7], PGC PTSD Workgroup[1]

[1]University of California San Diego, [2]University of Cape Town, [3]Stanford University, [4]Columbia University, [5]McLean Hospital, [6]University of Michigan, [7]Harvard School of Public Health

Background: Development of post-traumatic stress disorder (PTSD) is influenced by both genetic and environmental factors. The Psychiatric Genomics Consortium for PTSD (PGC-PTSD) has the goal to uncover the genetic architecture of PTSD with well-powered studies and deep phenotyping. We have now assembled over 55 cohorts worldwide, including over 20,000 PTSD cases and 60,000 controls. We present findings from genome-wide association studies (GWAS) and present novel methods to address heterogeneity across ancestry, gender, and trauma.
Methods: PTSD GWAS were performed within European, African, and Latino ancestry groups and trans-ethnic analyses used methods optimized for admixed and heterogeneous populations. Ancestry deconvolution was performed on admixed samples and association analyses were performed across ancestry-matched segments. SNP-based heritability and genetic correlations across PTSD studies and other psychiatric disorders and traits were calculated.
Results: Stratified analyses showed genome-wide significant hits in the European (chromosomal bands 6q25; p = 3.1x10-9 and 13q32; p = 2.7x10-8) and African ancestry groups (13q21; p = 3.8x10-8), and evidence for association in the smaller Latino ancestry groups, while trans-ethnic analyses remained non-significant. Findings were further supported using ancestry-deconvoluted segments. Significant heterogeneity was found between ancestry, sex and/or trauma type. Substantial genetic overlap of PTSD with other psychiatric disorders and traits, including age at first birth, MDD and schizophrenia were confirmed.
Conclusions: GWAS across a large number of representative studies show that PTSD development is appreciably influenced by genetic factors which overlap with other traits. Significant findings are ancestry-specific and require future investigation and replication.
Supported By: R01MH106595
Keywords: PTSD, GWAS, Ancestry

158. Exploring the Common Genetic Architecture of PTSD Symptoms in the UK Biobank

Gerome Breen[1] and **Jonathan Coleman**[1]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London

Background: UK Biobank have collected genome-wide genetic data and a wide range of health-related phenotypic data on 500,000 older adults from the UK population. Approximately 157,000 participants completed a follow-up mental health questionnaire, including items assessing symptoms of PTSD. We performed genomic analyses on a continuous measure of PTSD symptoms in 126,023 individuals.
Methods: Items derived from the abbreviated PTSD checklist (PCL6) were combined to define a continuous phenotype. Genome-wide association analysis, heritability estimation and genetic correlations with external phenotypes were calculated, as well as additional analyses assessing gene-level associations and gene set analyses.
Results: GWAS analyses identified an association with PTSD symptoms near the MHC region of chromosome 6. SNP-captured heritability was 7%, and genetic correlations were observed across a number of psychiatric phenotypes, particularly depression and anxiety.
Conclusions: PTSD symptoms show genetic continuity with psychiatric illnesses in general, and with depression and anxiety in particular. Examining symptoms as a continuous phenotype is a valuable approach to increasing power for genetic analyses.
Supported By: NIHR
Keywords: PTSD, GWAS, SNP-Based Heritability, Genetics

159. GWAS of PTSD Re-experiencing Symptoms in the VA Million Veteran Program

Murray Stein[1], Joel Gelernter[2], Hongyu Zhao[2], Ning Sun[2], Robert Pietrzak[3], Kelly Harrington[4], Kelly Cho[4], Jacqueline Honerlaw[4], Rachel Quaden[4], J. Michael Gaziano[4], and John Concato[2], Million Veteran Program MVP

[1]University of California, San Diego, [2]West Haven VA Medical Center, [3]VA National Center for PTSD, [4]BOSTON CSPCC / MAVERIC

Background: Posttraumatic stress disorder (PTSD) is a major public health problem which is presently poorly understood from a biological perspective. Genome-wide association studies (GWAS) provide an opportunity to discover and validate genetic risk factors for PTSD and its component phenotypes. Re-experiencing symptoms are characteristic and prototypical of PTSD and, as such, can serve as an important and informative phenotype for GWAS. The VA Million Veteran Program (MVP) has been building one of the world's largest medical and genetic information databases, and has included measurement of re-experiencing symptoms among their self-report measures.
Methods: We conducted a GWAS on the re-experiencing symptom cluster score based on a sum of 5 items from the PTSD Checklist (recurrent intrusive thoughts/dreams/flashbacks of trauma; emotional or physiological response to reminders of trauma), total score, 5-25.
Results: After data cleaning, 146,660 European-Americans (EAs) and 19,983 African-Americans (AAs) were retained. In the EAs, 8 distinct common-variant genomewide-significant (GWS) regions were identified—three with significance >5x10E-10. These latter regions map to chrom. 3 – lead SNP rs2777888 (2.1E-11), gene CAMKV, same SNP previously implicated in "age at first birth"; chrom. 17 – lead SNP rs2532252 (4.5E-10), closest to KANSL1 but within a long high-LD region that also includes CRHR1 (corticotropin releasing hormone receptor 1); and chrom. 18 – lead SNP rs2123392 (5.4E-11), at TCF4, previously GWS-associated to schizophrenia.
Conclusions: These data provide the first robust genomewide associations for a core PTSD endophenotype, reexperiencing. Additional bioinformatic analyses and attempts at replication will be needed to fully exploit and understand these findings.
Supported By: VA Cooperative Studies Program and VA Million Veteran Program
Keywords: PTSD - Posttraumatic Stress Disorder, Endophenotype, GWAS

160. Multivariate Approaches to Complex Genetic Phenotypes: Anxiety Disorders & PTSD

John Hettema[1] and Bradley Verhulst[2]

[1]Virginia Commonwealth University, [2]Michigan State University

Background: Many psychiatric disorders have high lifetime comorbidity partially explained by shared genetic risk. Multivariate phenotypic approaches applicable to psychiatric genome-wide association studies (GWAS) are recently available. However, most cross-disorder analyses have not applied such methods prior to conducting genetic association analyses.
Methods: We applied latent trait methods to characterize the high comorbidity of five DSM-based anxiety disorders to create a more informative phenotypic input to GWAS. We conducted GWAS meta-analyses in over 18,000 individuals of European ancestry from seven large, independent studies. We applied and compared two phenotypic approaches: (1) traditional comparisons between categorical anxiety disorder cases and super-normal controls, and (2) quantitative phenotypic factor scores derived from a multivariate analysis combining information across the clinical phenotypes.
Results: Each meta-analysis identified a different genome-wide significant region, with the following markers showing the strongest association: for case-control contrasts, rs1709393 located in an uncharacterized non-coding RNA locus on chromosomal band 3q12.3 (P=1.65x10-8); for factor scores, rs1067327 within CAMKMT encoding the calmodulin-lysine N-methyltransferase on chromosomal band 2p21 (P=2.86x10-9). Replication studies are underway in independent samples.
Conclusions: This approach has proven successful in our initial anxiety disorder GWAS. We outline extensions of this method that allow disaggregation of common versus disorder-specific risk. We propose how such methods may inform research aimed at elucidating the complex phenotypic and genetic structure of PTSD and its relationship to the anxiety disorders.
Supported By: NIH 1R01MH113665
Keywords: Anxiety Disorders, PTSD - Posttraumatic Stress Disorder, Genome-Wide Association Study, Multivariate Analysis, Psychiatric Comorbidities

SYMPOSIUM
Is the ClockΔ19 Mouse a Valid Model for Bipolar Disorder?

3:00 p.m. - 5:00 p.m.
Chair: Soren Dinesen Ostergaard

161. The Clock Protein Regulates Neuronal Maturation and Function in the mPFC

Colleen McClung[1], Jennifer Burns[1], Puja Parekh[1], and Kafui Dzirasa[2]

[1]University of Pittsburgh Medical Center, [2]Duke University Medical Center

Background: Bipolar disorder often manifests during adolescence and is thought to involve abnormal neuronal development. At the same time, bipolar disorder is associated with disruptions in circadian rhythms. However, little is known about the role of circadian genes in neuronal development through adolescence and how disruptions to this system impacts cognitive, mood and reward-related circuitry.
Methods: In these studies we used mice which have a mutation in the Clock gene. We performed a number of electrophysiological, molecular and behavioral analyses.
Results: We find that the loss of Clock function results in profound changes in the development of prefrontal cortical microcircuitry. Specifically, GABAergic interneurons that express parvalbumin (PV) normally show an increase in PV expression (P<0.05) and perineural net formation from P20-P90, indicative of neuronal maturation. In contrast, Clock mutants have a progressive decrease in PV expression and fail to show maturation in perineuronal nets. These changes are

associated with increased oxidative stress ($P<0.05$) specifically in PV cells across adolescence. In correlation with these changes, the mice display manic-like behavior, as well as electrophysiological changes indicative of altered oscillatory activity and altered synaptic plasticity which results in decreased glutamatergic signaling.
Conclusions: We find that disruption of the Clock gene has a particularly strong impact on the function and maturation of PV expressing interneurons in the mPFC. These studies help define the consequences of circadian clock disruption to neuronal maturation and function across adolescence into adulthood, and shed light on how clock disruption may be associated with the development of bipolar disorder.
Supported By: R01MH106460; NARSAD; R01DA039865; R21DA037636
Keywords: Circadian Rhythms, Bipolar Disorder, Oxidative Stress, Mouse Model

162. Face and Predictive Validity of the ClockΔ19 Mouse as an Animal Model for Bipolar Disorder: A Systematic Review

Mette Kristensen[1], Andrew A. Nierenberg[2], and **Soren Dinesen Ostergaard**[1]

[1]Aarhus University, [2]Harvard Medical School

Background: Mice carrying the Circadian Locomotor Output Cycles Kaput delta 19 N-ethyl-N-nitrosoure (ENU) mutation (ClockΔ19) are used as an animal model for bipolar disorder (BD). The aim of this study was to conduct a systematic review of the face validity (pathophysiological and phenotypic resemblance with BD) and predictive validity (responsiveness to BD treatments) of the ClockΔ19 mouse as an animal model for BD.
Methods: We performed a systematic search of PubMed and Embase, combining search terms covering ClockΔ19 and BD. The following inclusion criteria were employed in the study selection: I) Published in a peer-reviewed journal, II) Reports on original data, III) Contains information on the face or predictive validity of the ClockΔ19 mouse as a model for BD.
Results: The systematic search provided 1,281 records of which 22 met the predefined inclusion criteria. The results of the included studies show that the ClockΔ19 mouse is characterized by hyperactivity, decreased depression-like behavior, decreased anxiety-like behavior and increased preference for rewarding stimuli. This is highly consistent with human mania. Chronic administration of lithium, a drug with well-established mood-stabilizing effect in patients with BD, reverses the majority of the bipolar-like traits and most of the neurobiological abnormalities of the ClockΔ19 mouse.
Conclusions: This systematic review shows that the ClockΔ19 mouse has considerable face validity as an animal model for BD. The predictive validity of the ClockΔ19 has primarily been investigated by means of lithium challenge. Therefore, further studies are needed to determine how the ClockΔ19 mouse responds to other mood-stabilizing treatments.
Supported By: The Lundbeck Foundation
Keywords: Bipolar Disorder, Mania, Animal Model, Lithium, Predictive Validation

163. Utility of the Clock Mutant Mouse Model of Mania as a Tool for Drug Discovery

Ryan Logan[1], Angela Ozburn[2], Rachel Arey[3], Xiyu Zhu[4], Ethan Fitzgerald[4], and Colleen McClung[4]

[1]University of Pittsburgh School of Medicine, [2]Oregon Health & Science University, [3]Princeton University, [4]University of Pittsburgh

Background: The Clock mutant mouse has face, predictive, and construct validity for bipolar mania, and our laboratory has used these mice as a tool for discovering putative therapeutic targets of lithium and valproate, in addition to investigating the therapeutic efficacy of novel compounds. In particular, valproate, commonly prescribed for mood stabilization, directly inhibits histone deacetylases (HDACs), epigenetic enzymes modulating gene transcription. Our studies investigated whether valproate normalized the mania-like behaviors of the Clock mutant mouse in an effort to identify novel therapeutic targets and potentially relevant cellular and molecular mechanisms.
Methods: Male and female wild-type and Clock mutant mice underwent treatment with valproate, or other compounds with specific HDAC inhibitory activity (SAHA, class I and IIb; MS275 or ACY975, class I; and MC1568, class IIb), followed by anxiety-like (elevated plus maze, dark-light box, and open-field) and depressive-like (forced swim test, learned helplessness) behaviors. Additional cohorts of mice underwent behavioral testing following shRNA viral-mediated knockdown of class I HDACs, Hdac1 or Hdac2, or over-expression of HDAC2 (HDAC2OX) in the brain.
Results: Inhibition of class I HDACs (pharmacologically or knockdown) normalized anxiety-like and depressive-like behaviors of Clock mutant mice, recapitulating the effects of valproate and SAHA. Knockdown of Hdac2 in the brain also normalized these behaviors, while HDAC2OX prevented the behavioral effects of valproate in Clock mutant mice.
Conclusions: Together, our studies suggest valproate may exert therapeutic effects through HDAC inhibition, supporting the use of targeted inhibitory compounds for mood stabilization. Additional studies are beginning to elucidate the cellular and molecular mechanisms mediating these effects.
Supported By: NARSAD; NIMH R01MH106460
Keywords: Bipolar Disorder, Circadian Rhythms, Valproate, HDAC Inhibitors

164. Behavioral Assessment of Clock Mutant Mice: Consistencies and Contrasts With Bipolar Disorder

Jared Young[1] and Jordy van Enkhuizen[1]

[1]UCSD

Background: Bipolar disorder (BD) is known for patients cycling between mania and depressive states, though its cardinal feature is mania. Circadian rhythm disruptions exist in BD, evidenced by disturbed sleep cycle and that social rhythm therapy improve symptoms. Circadian rhythms are entrained via several proteins including CLOCK. Exon 19 deletion in the CLOCK gene (ClockΔ19

mice), results in 'mania-like' abnormal behaviors. Such circadian rhythm abnormalities may underlie observations that switches to mania are more likely in spring/summer, while depression occurs in fall/winter. ClockΔ19 mice may reveal mechanisms contributing to seasonality and/or behavior of BD mania.
Methods: Male and female ClockΔ19 mutant (mt) and wild-type (WT) mice (n=72) were used throughout testing in the Behavioral Pattern Monitor (BPM), prepulse inhibition (PPI), and forced swim testing (FST) after winter- (SA) vs. normal-active (NA) photoperiod conditions.
Results: Mt mice were hyperactive ($F(1,70)=19.8, p<0.0001$), and exhibited greater exploration ($F(1,70)=5.9, p<0.05$), though fewer initial holepokes ($F(2,140)=5.4, p<0.01$) vs. WT. Mt mice moved in more circumscribed patterns vs. WT mice ($F(1,70)=4.6, p<0.05$). Mt mice also exhibited poorer PPI ($F(1,22)=8.4, p<0.01$). Mt mice exhibited reduced FST immobility ($F(1,41)=39.0, p<0.001$). SA photoperiod increased FST immobility irrespective of genotype ($F(1,41)=4.1, p<0.05$).
Conclusions: Mt mice exhibit hyperactivity and partial specific exploration in the BPM, similar to BD mania. These mice exhibited more circumscribed locomotor patterns however, opposite to straight-line movement of BD patients. Additionally, these mice did not exhibit a hypersensitivity to altered seasonal photoperiods, unlike BD sufferers. Hence, while these mice recreate aspects of BD, they fail to recreate several behavioral disturbances of patients.
Supported By: R01MH104344
Keywords: Bipolar Disorder, Seasonal, Mania, Depression, Translational Research

SYMPOSIUM
Sleep as a Biomarker and Treatment Target for Substance Use Disorders
3:00 p.m. - 5:00 p.m.
Chair: Patrick Skosnik

165. Modulation of Sleep and Circadian Rhythm in the Treatment of Cocaine Use Disorder

Peter Morgan[1]

[1]Yale University School of Medicine

Background: Abnormal and poor sleep is characteristic of chronic cocaine users, who often do not recognize their sleep deficits. These deficits, including substantially reduced slow-wave or N3 sleep, contribute to cognitive problems and may promote ongoing use and relapse. Understanding the nature of these deficits may promote the identification of better treatment interventions for persons with cocaine use disorders, and reversing those deficits may be effective as treatments if the deficits are responsible for ongoing use or relapse.
Methods: To this end we studied 57 cocaine dependent participants who were randomized to receive modafinil 400mg (N=30) or placebo (N=27) daily during a period of inpatient treatment followed by six weeks of outpatient treatment. Polysomnographic sleep recordings were performed during inpatient treatment prior to and after starting modafinil.
Results: Modafinil was associated with increased N3 sleep time ($p=0.002$) as well as an increase in the percent of cocaine-free urines (52% vs. 26%; $p=0.02$). Mediation analysis showed that the change in N3 sleep was associated with improved clinical outcome. Intriguingly, modafinil was also associated with improved adherence to a more regular diurnal schedule, and adherence to that schedule was associated with longer time to relapse.
Conclusions: These findings suggest that directed regulation of sleep architecture and circadian rhythm can reduce cocaine use and relapse to cocaine use.
Supported By: NIDA-R01
Keywords: Slow Wave Sleep, Cocaine, Circadian Rhythms, Novel Treatments

166. Targeting Sleep Disturbance in the Treatment of Cannabis Use Disorders

Ryan Vandrey[1], Alan Budney[2], Evan Herrmann[3], Nicolas Schlienz[1], Aidan Hampson[4], Michael Smith[1], and Maxine Stitzer[1]

[1]Johns Hopkins University School of Medicine, [2]Dartmouth College, [3]Battelle, [5]NIDA

Background: Abrupt cessation of daily cannabis use reliably elicits withdrawal-induced insomnia, insomnia is a barrier to cessation, and extended-release zolpidem can attenuate abstinence induced sleep dysfunction. A clinical trial was conducted to evaluate extended-release zolpidem for improving clinical outcomes among those seeking treatment for cannabis use disorder (CUD).
Methods: A placebo controlled clinical trial of nightly extended-release zolpidem as an adjunct to psychosocial therapy among individuals seeking treatment for CUD (N=121) was conducted. Cannabis use and sleep assessments were obtained prior to and during a 12-week trial. Medication was self-administered nightly for 10 weeks followed by a 2-week taper. The blind on this study was broken just 5 days ago, so only qualitative results are presented, but inferential statistics will be conducted.
Results: There was no difference in study retention across medication groups. Among those retained in the study for at least 4 weeks (typical time required for daily cannabis users to obtain a clean urine with abstinence), 48% of those receiving zolpidem versus 33% receiving placebo had at least one negative urine, indicating sustained abstinence. Compared with pre-quit baseline, sleep latency measured by polysomnography the first week of treatment increased an average of 7 minutes for the active drug group compared with an increase of 49 minutes in the placebo group. Total score on the Insomnia Severity Index exhibited a greater reduction from baseline for active versus placebo throughout the study.
Conclusions: Initial outcomes suggest extended-release zolpidem may improve sleep and increase the probability of sustained abstinence among individuals seeking treatment for CUD.
Supported By: U01-DA031784
Keywords: Cannabis Use Disorder, Sleep, Treatment Outcomes

167. CBT-I Treatment for Insomnia in Alcohol Dependence: What Attributes Change With Treatment

Subhajit Chakravorty[1]

[1]Perelman School of Medicine University of Pennsylvania

Background: Insomnia is prevalent in about 65% of individuals with alcohol dependence (AD) in recovery and is associated with mood disturbance and an increased risk of relapse to drinking. Cognitive behavioral therapy for insomnia (CBT-I) is the recommended treatment for insomnia disorder and has shown promise in AD. The aim of this pilot study was to qualitatively evaluate the changes in sleep domains, psychiatric, alcohol use and neuro-behavioral assays with treatment.
Methods: A randomized, controlled trial of CBT-I in recovering alcohol dependent Veterans with insomnia. Subjects were allocated to either CBT-I (N=11) or Monitor-Only (MO, N=11) and treated for 8 weeks. Different assessment measures were used to assess sleep, psychiatric symptoms, alcohol, impulsivity and neurobehavioral measures. Linear mixed models adjusted for race evaluated the change over time across intervention arms. Stata 13.0 was used to conduct the analysis.
Results: All 22 subjects completed the 8 weeks of intervention. Treatment with CBT-I as compared to MO was associated with a superior improvement in insomnia severity index total score ($p<0.01$), sleep hygiene index total score ($p<0.05$), dysfunctional attitudes and beliefs scale total score ($p<0.05$), inventory of depressive symptoms scale total score (without the sleep items, $p<0.05$). A lower number of subjects relapsed to alcohol use and had lower alcohol craving scores in the CBT-I arm but these findings were not statistically significant. The analysis of the impulsivity and neurobehavioral assessments are currently ongoing.
Conclusions: CBT-I treatment in comparison to treatment-as-usual improves multiple insomnia-related clinical characteristics as well as depressive symptoms but not alcohol-related measures.
Supported By: Competitive Pilot Project Fund (VISN-4 VA) and VA grant IK2CX000855.
Keywords: Alcoholism, Insomnia, Depressive Symptoms, Alcohol Drinking, Impulsivity

168. The Effect of Fatty Acid Amide Hydrolase Inhibition on Sleep Architecture in Cannabis Withdrawal

Patrick Skosnik[1], Jose Cortes-Briones[1], Gina Creatura[1], Peter Morgan[1], Mohini Ranganathan[1], Emma Deaso[1], Toral Surti[1], and Deepak D'Souza[1]

[1]Yale University School of Medicine

Background: Cannabis Use Disorder (CUD) is now well-recognized, and is characterized by tolerance and withdrawal. Cannabis users who abruptly discontinue cannabis intake report sleep disturbances, which may contribute to relapse. To date, no approved treatments for CUD exist. Therefore, the current study examined whether the Fatty Acid Amide Hydrolase (FAAH) Inhibitor PF-04457845 would be efficacious in treating sleep disturbances in cannabis withdrawal by normalizing endocannabinoid tone.
Methods: Forty-one male individuals with CUD received either the FAAH-I (n=26) or placebo (n=15) daily for 4 weeks. Polysomnography (PSG) was performed at baseline when subjects were smoking as usual (Day -1), and during treatment (Days 0, 2, 4, 28). The primary dependent measures were time in stage REM, N1, N2, and N3.
Results: For N1, a main effect of day (Waldχ-2(4)= 12.790, $p<0.012$) and a group x day interaction was observed (Waldχ-2(4)=9.958, $p<0.041$). Pairwise comparisons revealed a trend towards decreased time in N1 on day 0 in the FAAH-I group ($p<0.085$). While no differences were observed for N2, a significant group x day interaction was observed for N3 (Waldχ-2(4)=10.437, $p<0.034$). Pairwise comparisons revealed that the FAAH-I group exhibited increased time in N3 on day 0 ($p<0.1$) and day 2 ($p<0.001$). For REM, only a main effect of day was observed (Waldχ-2(4)=20.478, $p<0.000$).
Conclusions: This study demonstrated that disruptions in stage N3 sleep during cannabis withdrawal could be reversed via FAAH inhibition. Thus, withdrawal-induced slow wave sleep disturbances could play a key role in relapse, and treatment via FAAH inhibition may be useful in maintaining abstinence from cannabis.
Supported By: U01 DA033267
Keywords: Cannabis Use Disorder, Marijuana, Sleep Disturbances, Cannabinoids, Sleep

SYMPOSIUM
Convergent Evidence From Genomic, Cell, and Brain Imaging and Post Mortem Studies on Myelination Abnormalities in the Psychotic Disorders

3:00 p.m. - 5:00 p.m.
Chair: Bruce Cohen
Co-Chair: Dost Ongur

169. The Reduced Myelination Observed in Schizophrenia in Vivo Correlates With Reduced Development of Oligocytes in Vitro

Dost Ongur[1], Donna McPhie[1], Fei Du[1], and Bruce Cohen[1]

[1]McLean Hospital/Harvard Medical School

Background: There is convergent in vivo, postmortem, and genomic evidence of abnormal oligodendrocyte development and function and diffusely lower myelin content in the brain in SZ. Our overall hypothesis is that oligodendrocyte abnormalities studied in culture will correlate with reduced myelination and abnormal connectivity measured in vivo.
Methods: We used a 4 Tesla Varian MRI scanner to collect magnetization transfer ratio (MTR) data in a 3x3x1cm voxel in the frontal white matter. MTR primarily reflects myelin content in white matter. We obtained biopsies for fibroblasts from 6 Healthy Control and 6 SZ patients from subjects who had undergone MTR imaging, and these lines were reprogrammed to iPS lines. iPSC were subsequently converted to oligodendrocyte rich cultures using a standard differentiation protocol.
Results: All cell lines expressed the oligodendrocyte markers SOX10, Olig2, NKX2.2, O4, O1, and MBP, but we observed a significantly lower number of O4 positive cells in SZ (F1,10=8.06,

$p<0.02$) at all days of culture. We also observed a trend for correlation between white matter MTR values and number of O4 positive cells at all time points ($p=0.07$) in 5 cases and 6 control subjects. (One subject had no available MTR value).
Conclusions: There is a significant correlation between generation of oligodendrocytes from patient-derived fibroblasts and myelin content measured using MRI in the same patients. The findings suggest that the mechanisms underlying reduced myelination in SZ in vivo may be studied in cell culture in vitro.
Supported By: Departmental funds
Keywords: Oligodendrocytes, Myelin, MRI, Schizophrenia

170. Genetic Pathway Analysis to Characterize the Role of Glia in Psychosis

Laramie Duncan[1], Peter Holmans[2], Colm O'Dushlaine[3], Phil Lee[4], Jordan Smoller[4], Dost Ongur[5], and Bruce Cohen[5]

[1]Stanford University, [2]Cardiff University, [3]Regeneron Genetics Center, [4]Harvard Medical School / MGH, [5]Harvard Medical School / McLean Hospital

Background: Large-scale genetic analyses, such as genome-wide association studies (GWAS), have been highly successful, and suggest that there are thousands of genetic risk variants for schizophrenia. Like many other complex genetic phenotypes, each genetic variant has a small impact on population risk (i.e. each variant explains less than half of one percent of phenotypic variance in schizophrenia). Pathway analysis is a method of extracting biologically useful information from GWAS results. Here we present an investigation of glial pathways in psychosis (in schizophrenia and bipolar disorder) using established pathway analysis methods, and we also present a framework for refining pathway analysis methods.
Methods: Data from the Psychiatric Genomics Consortium PGC were used for all analyses. For schizophrenia we used 9,394 cases and 12,462 controls and for bipolar disorder we used 7,481 cases and 9,250 controls. MAGMA, DEPICT, and other pathway analysis methods were used for pathway analysis.
Results: The Glia-Oligodendrocyte pathway was associated with schizophrenia using three pathway analysis methods (minimum $p = 0.0005$). A framework for improving mapping of genetic variants to genes, and for testing the effect of such improvements on pathway analysis results, is presented.
Conclusions: Consistent with findings of white matter abnormalities in schizophrenia by other methods of study, the Glia-Oligodendrocyte pathway was associated with schizophrenia in our genomic study. These findings suggest that the abnormalities of myelination observed in schizophrenia are at least in part due to inherited factors. Improvements in pathway analysis can help to identify relevant biological processes, and guide future translational research.
Supported By: Jonathan Edwards Brooking Memorial Fund for Mental Health Research at McLean Hospital & National Institute of Mental Health (NIMH) grant T32MH017119; JWS – National Institute of Mental Health (NIMH) grant K24MH094614; DO - NIMH grant R21MH096107-01A1; BMC – Maltz Distinguished Investigator Award, National Alliance for Research on Schizophrenia and Depression (NARSAD).
Keywords: Psychosis Phenotype, Genetics, Glia

171. Combined Neuropathological, Genetic and Imaging Approaches Reveal Myelination Abnormalities in Schizophrenia

Nora Perrone-Bizzozero[1], Vincent Calhoun[2], Yue Feng[3], Jingyu Liu[4], and Jessica Turner[5]

[1]University of New Mexico, School of Medicine, [2]Mind Research Network University of New Mexico, [3]Emory University, [4]The Mind Research Network, [5]Georgia State University

Background: Increasing evidence indicates that myelin/oligodendrocyte abnormalities contribute to the pathophysiology of schizophrenia. Our group initially identified alterations in the myelination marker MBP in schizophrenia (SZ) and bipolar disorder (BP). Subsequent work examined genetic contributions to white matter (WM) alterations using molecular and neuroimaging methods.
Methods: Post-mortem tissue studies measured single nucleotide polymorphisms (SNP) and QKI isoform mRNA levels by genotyping and real time RT-PCR assays, respectively. Independent Component Analyses (ICA) of diffusion tensor images (DTI) and SNP arrays were used to delineate genetic contributions to fractional anisotropy (FA) changes in SZ. Statistical analyses included MANCOVAs and linear regressions of ICA coefficients vs. genotype. All p values were adjusted using Bonferroni corrections.
Results: To examine genetic factors contributing to myelin alterations, we first focused on a SZ-associated SNP in QKI, a gene encoding a critical factor for CNS myelination. RT-PCR analyses revealed significant alterations ($p=0.0307$) in QKI isoform ratios associated with this SNP in the corpus callosum of SZ but not BP patients. To further study the effect of SNPs in WM structure, we obtained DTI and genome-wide SNP data from 74 SZ cases and 87 matched-controls. We found that a SNP in GRM3 shows a significant association ($q=0.0249$) with decreased FA values in cortico-cerebellar-thalamic-cortical circuits of patients but not controls.
Conclusions: Given that QKI and GRM3 are both expressed in oligodendrocyte precursor cells and developmentally regulated, our findings suggest that dysfunction of these genes may underlie myelination deficits in schizophrenia and provide novel targets for therapeutic interventions.
Supported By: 1RC1MH089257 and R01EB005846
Keywords: Intracortical Myelination, Genetic Association, Oligodendrocytes, Structural Neuroimaging, Human Postmortem Brain

172. Receptor Protein Tyrosine Phosphatases in Schizophrenia

Dolores Malaspina[1], Thorsten Kranz[2], Oded Gonen[2], Sheila Harrock[3], and Moses Chao[2]

[1]Mount Sinai School of Medicine of the City University of New York, [2]NYU Medical Center, [3]Mount Sinai School of Medicine

Background: Receptor protein tyrosine phosphatases, gamma (PTPRZ) and zeta (PTPRG), are cell surface ligands for contactin molecules, they bind with Contactins and are crucial for cell adhesion, signaling and neurodevelopment. Their main expression is in microglia and neurons, respectively; PTPRZ is essential

for recovery from neuroinflammation. Both regulate neurotransmitter receptor function and are genetically associated with schizophrenia, affective disorders, Alzheimer's and autism.
Methods: Following identification of a de novo null PTPRG mutation in a sporadic schizophrenia case, we modeled their loss-of-function mutations using knockouts (KO), comparing PTPRG−/− PTPRZ−/− to wild-type male mice and examined the effect of PTPRG rare variants in schizophrenia cases, including the imaging of the entire hippocampus with 3D multivoxel 3T 1H-MRS.
Results: PTPRZ-KO mice had marked aggression and PTPRG-KO had reduced immobilization in the forced swim test. Both had greatly elevated PFC, hippocampus and amygdala dopamine levels with decreased amygdala dopamine beta hydroxylase activity; only the PTPRG-KO distinctly showed increased hippocampal 5HT.10% of cases in a series harbored rare/novel variants of PTRPG. These had an earlier onset of severe psychosis, childhood learning disabilities and specific cognitive deficits in working memory, despite higher intelligence scores. Imaging showed the highest Cho concentrations in these cases, which predicted both psychotic (.590, p=.021) and manic symptoms (.686, p=.005), consistent with demyelination, but unassociated with volume.
Conclusions: These data are consistent with an inflammatory hippocampal pathology predicting more severe active symptoms with compromised PTPRG activity producing active symptoms. PTP are important molecules for pharmaceutical research.
Supported By: NIMH
Keywords: Knock-Out Mouse Hippocampus PTPRG, Schizophrenia, Translational

SYMPOSIUM
Neuroimaging Biomarkers of Treatment Outcome and of Antidepressant Effects in Major Depressive Disorder
3:00 p.m. - 5:00 p.m.
Chair: Jeffrey Miller

173. PET Imaging Matching Major Depression Pathophysiology and Antidepressant Treatment Target

J. John Mann[1], M. Elizabeth Sublette[2], Maria Oquendo[3], Jeffrey Miller[2], Todd Ogden[4], Ramin Parsey[5], Francesca Zanderigo[6], and Mate Milak[2]

[1]NY State Psychiatric Institute, [2]Columbia University, [3]University of Pennsylvania, [4]Columbia University & New York State Psychiatric Institute, [5]Stony Brook University School of Medicine, [6]New York State Psychiatric Institute, Columbia University Medical Center

Background: Identified brain pathophysiology in major depressive disorder (MDD) as a target for antidepressant action is a rational approach to antidepressant treatment development. We identified a trait elevation of autoreceptor expression on serotonin neurons in MDD. More autoreceptors cause less serotonin neuron firing and serotonin release in a mouse model.

SSRIs reduce number and responsiveness of these autoreceptors in rodents, thereby increasing serotonin firing and release, over weeks, their main mechanism of action. Parallel depressed human subject studies are needed.
Methods: Twenty-four depressed MDD subjects and 51 healthy control subjects underwent positron emission tomography scanning with [11C]WAY-100635 to estimate 5-HT1A binding potential. MDD subjects received 8 weeks of escitalopram. A separate group of 19 patients with MDD had two scans, before and after a mean of 7 weeks of SSRI treatment.
Results: Escitalopram remitters had 33% higher baseline 5-HT1A binding in the raphe nuclei than nonremitters ($p = .047$). Across 12 cortical and subcortical regions, 5-HT1A binding did not differ between remitters and nonremitters ($p = .86$).

In the group scanned before and after SSRI treatment, an 18% decrease in autoreceptor binding was observed accompanied by a 52% decrease in HAMD scores.
Conclusions: SSRIs effectiveness for depression appears to be related to the degree of elevation in autoreceptors prior to treatment and to the downregulation with treatment. Accelerating the effect on autoreceptors remains a viable method for accelerating onset of antidepressant action in depression.
Supported By: NIMH
Keywords: Unipolar Major Depression, Serotonin 1A Receptor, SSRI

174. Neuroimaging Correlates of Antidepressant Response to Ketamine

Elizabeth Ballard[1]

[1]NIH/NIMH

Background: Ketamine has been associated with rapid antidepressant effects, but the neural correlates of the response remain unknown. Multimodal imaging techniques in both patient and healthy samples may elucidate the mechanism of ketamine's antidepressant response.
Methods: Results will be presented from the NIMH Ketamine Mechanism of Action Study (MOA), in which a sample of 35 unmedicated patients with treatment-resistant MDD and 25 healthy controls (HCs) underwent a double-blind, placebo-controlled, randomized cross-over trial of ketamine. Neuroimaging scans (3T fMRI and MEG) were completed before and after both ketamine and placebo infusions. Specific results from an emotional dot-probe task during fMRI, as well as resting state fMRI and MEG, will be presented.
Results: On fMRI, there was a differential BOLD response in the anterior cingulate cortex to an emotional dot-probe task after ketamine in MDD patients and HCs ($pFWE<0.001$). Specifically, brain activity in MDD patients after ketamine was similar to HCs after placebo, suggesting a normalization of function. Similarly, resting state functional connectivity on fMRI between the insula and the default mode network (DMN) was normalized in MDD patients compared to HCs post-ketamine infusion. On MEG, increased gamma power was found after ketamine in both MDD patients and HCs. Baseline gamma power moderated the relationship between antidepressant response and post-ketamine gamma power ($p=0.004$).
Conclusions: Results suggest that ketamine may reverse neural biases and alter functional connectivity commonly found in MDD. In using a HC comparison group, who also

received ketamine, it appears that ketamine may normalize patterns of neural activity to that seen in healthy populations.
Supported By: NIH IRP
Keywords: Ketamine, fMRI Resting State, MEG, fMRI

175. Cognitive Behavioral Therapy for Depression and the Neural Correlates of Emotion Regulation: Prediction of Treatment Outcome and Longitudinal Effects

Jeffrey Miller[1], Harry Rubin-Falcone[2], Jochen Weber[1], Ronit Kishon[2], Kevin Ochsner[1], Lauren Delaparte[3], Bruce Doré[4], Bryan Denny[5], Francesca Zanderigo[2], Maria Oquendo[4], and J. John Mann[2]

[1]Columbia University, [2]New York State Psychiatric Institute, Columbia University Medical Center, [3]Stony Brook University, [4]University of Pennsylvania, [5]Rice University

Background: Cognitive behavioral therapy (CBT) is effective for a substantial minority of patients with major depressive disorder (MDD), but its mechanism of action is unknown, and predictors of treatment outcome are lacking. As core techniques of CBT seek to enhance emotion regulation, we examined the neural correlates of emotion regulation using functional Magnetic Resonance Imaging (fMRI) before and after a course of CBT for MDD.
Methods: 31 unmedicated MDD participants underwent baseline fMRI scanning during tasks in which they engaged in a voluntary emotion regulation strategy during A) recall of negative autobiographical memories and B) presentation of emotionally aversive photographs. 23 participants completed scanning post-treatment. Treatment outcome was assessed using the Beck Depression Inventory and the Hamilton Depression Rating Scale. Image processing and statistical analyses were performed in FSL.
Results: While regulating responses to negative autobiographical memories, those with better treatment outcome showed post-treatment suppression of BOLD contrast in subgenual anterior cingulate, medial prefrontal cortex, and lingual gyrus clusters (voxel-wise $z>3.1$, FWE-corrected $p<0.05$). From the photographs task, greater pre-treatment BOLD responses to emotionally negative images in a cluster in hippocampus predicted worse treatment outcome (statistical thresholding as above).
Conclusions: CBT response may be mediated by enhanced downregulation of neural activity during emotion regulation; regions identified overlap with those found using a similar task in a normative sample, and are implicated in self-referential/emotion processing. Hippocampal activation during viewing of aversive images may reflect overgeneralization processes predisposing to poor treatment outcome. Future studies should examine the specificity of these effects to CBT.
Supported By: NIMH K08MH085061
Keywords: Cognitive Behavioral Therapy, Major Depression, fMRI, Emotion Regulation

176. Evidence of Differential Changes in Cortical Thickness and Volume Between SSRI and Placebo Treated Patients With Major Depressive Disorder

Elizabeth Bartlett[1], Christine DeLorenzo[2], Priya Sharma[2], Jie Yang[1], Mengru Zhang[1], Eva Petkova[3], Myrna Weissman[4], Patrick McGrath[5], Maurizio Fava[6], Todd Ogden[7], Benji Kurian[8], Ashley Malchow[8], Crystal Cooper[8], Joseph Trombello[8], Melvin McInnis[9], Phil Adams[5], Maria Oquendo[10], Diego Pizzagalli[11], Madhukar Trivedi[8], and Ramin Parsey[2]

[1]Stony Brook University, [2]Stony Brook University School of Medicine, [3]New York University Langone Medical Center, [4]College of Physicians and Surgeons, Columbia University, [5]New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, [6]Massachusetts General Hospital, [7]Columbia University & New York State Psychiatric Institute, [8]University of Texas Southwestern Medical Center, [9]University of Michigan, [10]University of Pennsylvania, [11]Harvard Medical School/McLean Hospital

Background: To date, clinical translation of biomarkers for major depressive disorder (MDD) treatment response has been limited. Development of noninvasive, MRI based biomarkers could allow for individualized treatment selection, reducing time spent on ineffective treatments and the cost burden of MDD.
Methods: Multisite pre- and early-treatment (1-week) T1-weighted structural MRI scans acquired from 184 MDD patients randomized to an 8-week trial of sertraline or placebo were analyzed. This study is the largest placebo-controlled effort to characterize pre- or early-treatment structural alterations, in an effort to predict antidepressant treatment response in MDD patients. To standardize measures, a novel data harmonization procedure, shown to improve the reproducibility of subsequent statistical analyses, was applied.
Results: Across the a priori regions (rostral and caudal anterior cingulate, lateral orbitofrontal, rostral middle frontal, and hippocampus) a robust region-specific differential treatment effect was found in pre- and early-treatment morphometry between the placebo ($N=97$) and sertraline ($N=87$) treated groups. Region-specific pre-treatment ($p=0.040$) and early-treatment changes in cortical thickness ($p=0.004$) and volume ($p=0.046$), differentially predicted clinical response between the treatment groups. Post-hoc analysis revealed that this effect was significant in the rostral middle frontal cortex in placebo-treated patients and in the rostral anterior cingulate cortex in sertraline-treated patients. Mediation and moderation analyses were further examined.
Conclusions: Overall, we revealed short-term morphometric alterations that differentially associated with antidepressant and placebo treatment response. These findings, obtained with a site harmonization method shown to boost statistical reproducibility, enhance our understanding of the anterior cingulate cortex's role in the SSRI mechanism of action.
Supported By: NIMH awards: U01MH092221 (Trivedi, M.H.) and U01MH092250 (McGrath, P.J., Parsey, R.V., Weissman, M.M.). Valeant Pharmaceuticals donated the Wellbutrin XL for use in this study.
Keywords: Structural MRI, Individualized Treatment, Major Depressive Disorder (MDD), Cortical Thickness, Anterior Cingulate Cortex (ACC)

Saturday, May 12, 2018

PLENARY
Moving Towards Translation
8:00 a.m. - 11:25 a.m.
Chair: Lori McMahon

177. Unmasking Biological Markers of Addiction Along the Path to Treatment Interventions

Yasmin Hurd

Icahn School of Medicine at Mount Sinai

The talk will provide insights about molecular neurobiological markers in mesocorticolimbic brain regions that appear to be characteristic of addiction and related comorbid psychiatric disorders. A translational scientific approach is taken from animal models and human neurobiological investigations to human clinical laboratory studies. She will discuss the potential of novel pharmacological targets of key biological marks that might function as therapeutic interventions.
Keywords: Cannabis, Drug Addiction, Epigenetics, Psychosis, Glutamate

178. Dysfunction of Kynurenic Acid in Major Psychiatric Diseases: Causes, Effects and Therapeutic Opportunities

Robert Schwarcz

Maryland Psychiatric Research Center

Kynurenic acid (KYNA) is an astrocyte-derived metabolite of the kynurenine pathway of tryptophan degradation and antagonist of alpha7 nicotinic acetylcholine and N-methyl-D-aspartate receptors, and its levels are elevated in the prefrontal cortex of individuals with schizophrenia. Because endogenous KYNA modulates extracellular glutamate, dopamine and GABA levels in the brain, these increases may be pathophysiologically significant. The presentation will review the latest insights into KYNA neurobiology and provide an update on translationally relevant efforts to manipulate KYNA levels in the mammalian brain.
Keywords: Astrocyte, Cognition, Kynurenic Acid, Schizophrenia, Tryptophan

179. The Potential and Limitations of Transcranial Direct Current Stimulation

Marom Bikson

The City College of The City University of New York

Few emerging therapies for neuropsychiatric disorders has engaged as much excitement and also debate as transcranial Direct Current Stimulation (tDCS). To identify the potential of tDCS and move beyond the hype, this talk addresses the technology and cellular foundations of tDCS. For decades, it has been established that direct current stimulation can modulate plasticity; new research is unraveling the cellular mechanisms of how direct current stimulation can produce nuanced and targeted changes in brain function. Over the past decade, the technology of tDCS has advanced from basic clinical stimulator using two electrodes to High-Definition tDCS (HD-tDCS) using arrays of electrodes and to Remove-Supervised technology for home use. These new technologies have allowed categorical enhanced in the targeting (HD-tDCS) and deployment (Remote-Supervised) of tDCS. Finally, new approaches to optimize tDCS using imaging and biomarkers, including used EEG reciprocity, have provided new insight on therapeutic mechanisms as well as rational methods to select patients and individualize tDCS. The thesis of this talk is that tDCS is grounded in well-established biophysical principles but that emerging technologies will support robust and efficacious translation to patients.
Keywords: tDCS, Neuromodulation, Depression, Pain, Neuropathic Pain

180. Time for a Change in Psychosis Research

Brett Clementz

University of Georgia

Among segments of the clinical and research communities there is palpable discontent with continued reliance on surface features alone for subgrouping psychosis cases. The uncertain differential diagnostic utility of clinical features has been known for some time. But there is continued uncertainty regarding optimal method(s) for defining psychosis subgroups to support optimal treatment and research missions. This presentation will review the history of this problem and propose a set of prescriptions for enhancing knowledge acquisition on the nature of the psychoses.
Keywords: Psychosis, Neurobiology, Hypothesis Testing, Classification, B-SNIP

181. Drug Addiction: The Gain in the Brain is in the Pain

George Koob

NIAAA National Institutes of Health

Addiction is a chronically relapsing disorder characterized by compulsive drug seeking that is hypothesized to derive from multiple sources of motivational dysregulation. The construct of negative reinforcement, defined as drug taking that alleviates a negative emotional state (hypohedonia, dysphoria, anxiety, hyperalgesia, irritability, and sleep disturbances) that is created by drug abstinence. The negative emotional state associated with addiction has been termed hyperkatifeia from the Greek “katifeia” for “dejection or sadness,” and is particularly relevant as a motivational driving force in both the withdrawal/negative affect and preoccupation/anticipation stages of the addiction cycle. The shift in motivation to negative reinforcement is termed the “dark side of addiction,” and is hypothesized to reflect an allostatic misregulation of hedonic tone such that drug taking makes the hedonic negative emotional state worse during the process of seeking temporary relief via compulsive drug taking. In animal models, repeated misuse of drugs of abuse results in negative emotion-like states reflected in increased reward

thresholds, decreased pain thresholds, anxiety-like and dysphoric-like responses. Such negative emotional states that drive negative reinforcement are hypothesized to derive not only from "within system" dysregulation of key neurochemical circuits that mediate incentive-salience/reward systems (dopamine, opioid peptides) in the ventral striatum but also from the" between system" recruitment of brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids and neuroimmune factors) in the extended amygdala. Excessive drug taking is also accompanied by deficits in executive function produced by neurocircuitry dysfunction in the medial prefrontal cortex that may facilitate the transition to compulsive-like responding and relapse. Thus, compelling evidence exists to argue that plasticity in the brain pain emotional systems is triggered by acute excessive drug intake, is sensitized during the development of compulsive drug taking with repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of compulsive drug seeking.

Keywords: Addiction

SYMPOSIUM
Top-Down Control of Sensory Processing: Relevance to Psychosis

12:30 p.m. - 2:30 p.m.
Chair: Hirofumi Morishita
Co-Chair: Jordan Hamm

182. Hallucinations Result From the Over-Weighting of Perceptual Priors

Philip Corlett

Yale University

Background: Some people hear voices that others do not, but only some of those people seek treatment. Those that need treatment are more distressed by their experiences. This is particularly acute for the 10-30% of patients with intractable hallucinations. There is a clear need for a deeper more mechanistic understanding of hallucinations. We can perhaps understand hallucinations in terms of an imbalance in this process such that prior beliefs are over-weighted and percepts are created where there should be none. We sought to test this hypothesis.
Methods: Using a Pavlovian learning task during functional neuroimaging, we induced conditioned hallucinations in four groups of people who differed orthogonally in their voice-hearing and treatment-seeking. We captured behavioral and brain responses to this training and analyzed those responses using a hierarchical computational model.
Results: People who hear voices (n=29) were more susceptible to the effect ($p<0.005$). We characterized a brain circuit, incorporating the anterior insula, superior temporal sulcus (STS) and auditory cortex that mediated the conditioned hallucinations ($p<0.05$ FDR corrected). Critically, voice-hearing participants over-weighted their priors (and this was associated with stronger insula and STS responses, $p<0.05$). Furthermore, people with a diagnosed psychotic illness (n=30) did not develop beliefs about task volatility and therefore did not update their priors ($p<0.05$).
Conclusions: We demonstrate a profound pathological impact of top-down processes on perception. It may represent an objective means to discern people with a need for treatment. In addition, this work may inspire new candidate treatments as well as means to match individuals to those treatments.
Supported By: NARSAD, IMHRO, NIMH R01
Keywords: Auditory Hallucinations, Computational Psychiatry, Functional Brain Imaging

183. The Role of Prefrontal Inputs to Visual Cortex in Biomarkers of Sensoricognitive Processing Deficits

Jordan Hamm[1], Yuriy Shymkiv[1], and Rafael Yuste[1]

[1]Columbia University

Background: Sensory stimuli are naturally perceived within a spatiotemporal context, wherein novel events are processed and repetitive elements ignored. Such contextual modulations of sensory processing are disrupted in schizophrenia, potentially undermining how individuals perceive and relate to a changing environment. Translational studies of biomarkers of context processing deficits (e.g."mismatch negativity") demonstrate a key role for local inhibitory circuitry in sensory cortices (e.g. V1), but because context integrates information about past and current regularities, larger brain networks involving prefrontal cortex (PFC) may be implicated as well.
Methods: With two-photon calcium imaging, optogenetics, and local field potential recordings in awake mice (n=16), we recorded and manipulated the dynamic activity of individual long-range PFC axons projecting to V1 during a visual oddball paradigm (84% redundant, 16% deviant visual stimuli).
Results: Robust visually driven responses were recorded in individual PFC axons (n=120), albeit showing slightly later activation (100ms; $p<.05$), suggesting a feedback role. Like V1 neurons, these inputs displayed "stimulus-specific adaptation" (i.e. reduced responses to redundant stimuli; $p<.01$) but, unlike V1 neurons, did not display clear "deviance detection" (i.e. enhanced responses to deviants). Optogenetic suppression of PFC axonal inputs to V1 eliminated deviance detection in V1 neurons (n=160 cells, $p<.05$) and related theta-band oscillations, but by disinhibiting all non-adapted visual responses regardless of context.
Conclusions: Disrupted top-down influence on sensory cortices could produce a state where non-adapted stimuli are erroneously processed as "deviants", potentially contributing to distractibility, cognitive dysfunction, and even delusions. This study provides a translational biomarker-driven approach for understanding the neuronal circuit-level deficits seen in schizophrenia.
Supported By: NIMH (K99MH115082-0; F32-MH106265, R01MH101218; R01MH100561)
Keywords: Prefrontal Cortex, Somatostatin Neuron, Parvalbumin Interneurons, Mismatch Negativity, Theta and Alpha Oscillations

184. Prefrontal Modulation of Visual Cortex as a Cross-Diagnostic Marker of Attentive Selection Propensity

Andreas Keil[1] and Lisa McTeague[2]

[1]University of Florida, [2]Medical University of South Carolina

Background: Aberrant selective attention has been proposed as a fundamental mechanism contributing to a range of psychiatric disorders. Research in the animal model has suggested that at the core of perceptual and attentional dysfunctions are exaggerated or diminished top-down biasing signals originating in prefrontal cortical regions. However, translating this research into work with human participants has been difficult because of methodological limitations.
Methods: The present sequence of three studies combines multi-modal imaging of EEG and fMRI with experiments using intracranial EEG, in healthy participants and patients diagnosed with anxiety disorders, to define the precise sources and targets of top-down bias signals when viewing stimuli differing in motivational (fear-) relevance for the observer. Directed connectivity analyses of electrophysiological and hemodynamic signals are conducted and validated against other measures such as onset latency and coherency.
Results: Across observers and three studies (Ns = 18, 16, and 104), viewing fear-relevant visual stimuli prompted greater signaling from prefrontal to visual areas (all ps $<$ .01, controlled for multiple comparisons), associated with sensory amplification of fear-relevant stimuli. Importantly, cross-diagnostic symptom severity predicted these differences in the patient sample, with prefrontal bias signaling for fear-relevant stimuli greatest in those with intermediate severity, and least pronounced in the most severely impaired patients.
Conclusions: These distinct patterns of prefrontal-to-visual bias signaling may provide a powerful means for personalizing neuroscience-based interventions to modify impairment/biases related to perceptual and attentional processes. They also represent an avenue towards a mechanistic dimension of impaired attention as specified in the NIMH's Research Domain Criteria framework.
Supported By: R01MH097320, R01MH112558
Keywords: Attention, Perception, Electrophysiology, Connectivity, Multimodal Imaging

185. A Developmental Circuit Milestone for Prefrontal Top-Down Control of Sensory Processing

Hirofumi Morishita

Icahn School of Medicine at Mount Sinai

Background: Long-range connectivity from prefrontal to sensory cortical regions develops into adulthood to enable complex top-down cognitive processes such as attention. Disruption of top-down control is increasingly identified in psychiatric disorders with neurodevelopmental origins, but the developmental steps that achieve functional long-range connectivity are poorly described. Here, we interrogate long-range cortico-cortical projection neuron development through complementary circuit-specific approaches in top-down prefrontal cortex neurons projecting to visual cortex in mice.
Methods: Circuit-specific electrophysiology, dendritic spine analysis, and monosynaptic input mapping were performed during adolescence and in adulthood in mice to examine an integration of local and long-range connectivity onto prefrontal projection to visual cortex in mice. Causal contribution of top-down projection neuron activity during development on attentional behavior was assessed by chemogenetically suppressing top-down neuron activity only during adolescence, followed by adult testing of visual attention by the five-choice serial reaction time task.
Results: Interrogation of long-range cortico-cortical projection neuron development through complementary circuit-specific approaches in mice revealed that a prefrontal top-down projection experiences an adolescent state of local hyper-connectivity that enables balanced integration of local and long-range connectivity. Failure to achieve this activity-dependent developmental milestone produces adult impairments in attention behavior. Further, post-adolescent expression of a cholinergic molecular brake of cortical plasticity is required to establish an optimal balance between local and long-range inputs essential for attentional behavior.
Conclusions: These findings propose "local/long-range input balance" as a key developmental milestone for cognitive development, and offer a novel conceptual framework for understanding of psychiatric and neurodevelopmental disorders, as well as strategies for therapeutic interventions.
Supported By: NIMH, NEI, NINDS
Keywords: Attention, Adolescence, Prefrontal Cortex, Visual Processing, Mouse Model

SYMPOSIUM
Rapid Acting Antidepressants, Ketamine, and Hydroxynorketamines

12:30 p.m. - 2:30 p.m.
Chair: Todd Gould
Co-Chair: Ronald Duman

186. Initial Cellular Trigger of Rapid Acting Antidepressants: Direct and Indirect Glutamatergic Mechanisms

Ronald Duman

Yale University School of Medicine

Background: Despite advances in our understanding of rapid antidepressant mechanisms, the initial cellular trigger underlying the actions of ketamine and other agents has not been determined. Notably, do rapid acting agents act directly on glutamatergic neurons or indirectly on GABAergic interneurons to produce antidepressant responses?
Methods: This question is being addressed using viral mediated shRNA expression for cell specific knockdown of GluN2B or M1-ACh receptors on GABA vs. glutamate neurons.

Results: The results demonstrate that knockdown of GluN2B on GABA, but not glutamate neurons in the medial PFC blocks the antidepressant actions of ketamine, as well as it's metabolite (2R,6R)-hydroxynorketamine (HNK) in the FST and NSFT. Similarly, knockdown of the M1-ACh receptor on GABA, but not glutamate neurons blocks the antidepressant actions of scopolamine. Surprisingly, the actions of GLYX-13 were blocked by knockdown of GluN2B on glutamate but not GABA neurons in the medial PFC, consistent with reports that GLYX-13 does not increase extracellular glutamate.
Conclusions: Together, these studies demonstrate that the initial trigger for ketamine, HNK and scopolamine is blockade of GABA neuronal firing resulting in disinhibition of glutamate, while the initial trigger for GLYX-13 is GluN2B on pyramidal neurons; in all cases the end result is increased synapse formation on glutamate pyramidal neurons, resulting in rapid and sustained antidepressant effects. Further studies are being conducted to determine the type of GABA interneuron that mediates the actions of ketamine and HNK, and to further distinguish the mechanisms underlying the antidepressant vs. side effect profile of ketamine compared with HNK.
Supported By: This research was supported by National Institute of Mental Health grants MH093897 and MH105910 and by a research grant from Allergan.
Keywords: Ketamine, Hydroxynorketamine, Scopolamine, GLYX-13, GABAergic Interneurons

187. Ketamine Metabolism to Hydroxynorketamines: Relevance to Fast Antidepressant Action

Todd Gould

University of Maryland School of Medicine

Background: The widespread clinical use of ketamine as an antidepressant is limited due to its abuse liability and capacity to produce dissociative effects. Ketamine's mechanism of antidepressant action has been hypothesized to be due to NMDAR inhibition; however, other NMDAR antagonists do not manifest the full antidepressant actions of ketamine. Ketamine is rapidly and stereospecifically metabolized to norketamine, dehydronorketamine, hydroxyketamine and the hydroxynorketamines (HNKs).
Methods: Using mouse tests of antidepressant efficacy, we assessed the antidepressant and anti-anhedonic effects of ketamine's enantiomers and its hydroxynorketamine metabolites. We also performed in vitro field excitatory post-synaptic potential (fEPSP) measurements, western blot analysis, and in vivo electroencephalogram measurements of gamma power as an in vivo measure of target engagement. Side effects of ketamine and its metabolites were assessed.
Results: Our experiments demonstrated that production of the (2S,6S;2R,6R)-hydroxynorketamine metabolite is essential for ketamine's sustained antidepressant effects and found that the (2R,6R)-HNK enantiomer exerts behavioral, electroencephalographic, electrophysiological, and cellular antidepressant and anti-anhedonic actions in vivo that require early and sustained AMPA receptor activation. (2R,6R)-HNK did not exert ketamine-associated discriminative properties abuse potential, sensory dissociation or locomotor stimulant side effects, consistent with weak activity at the NMDAR, indicating a safer side effect profile compared to ketamine.
Conclusions: Our results indicate a novel mechanism underlying ketamine's unique antidepressant properties, which involves the required activity of a distinct metabolite. Considering the lack of side effects these findings have relevance for the development of next generation, rapid-acting antidepressants.
Supported By: MH107615
Keywords: Ketamine, Hydroxynorketamine, Antidepressant Action, Hippocampal Neuroplasticity, Glutamate

188. Common Neurotransmission Recruited in Ketamine and (2R,6R)-Hydroxynorketamine-Induced Sustained Antidepressant Effects

Alain Gardier[1], Thu Ha Pham[1], Céline Defaix[1], Xiaoming Xu[2], Shi-Xian Deng[2], Nicolas Fabresse[3], Jean-Claude Martinez[3], Rebecca A. Brachman[2], and Christine A. Denny[2]

[1]Univ Paris-Sud Fac Pharmacie, [2]Columbia University, [3]Lab. Pharmacologie, Hôpital Garches

Background: (R,S)-ketamine unlikely exerts its antidepressant-like activity solely via NMDA receptor blockade. We previously found a correlation between (R,S)-ketamine-induced increase in cortical serotonin (5-HT) release and its antidepressant-like activity in mice. By stimulating AMPA receptors in Rodents brain, (2R,6R)-hydroxynorketamine (HNK), a major active metabolite, would be essential for ketamine antidepressant-like activity. We hypothesized that this activity is mediated by the regulation of synaptic excitatory/inhibitory balance and concomitant changes in glutamate/GABA neurotransmission induced by both (R,S)-ketamine and (2R,6R)-HNK in rodents brain.
Methods: (R,S)-ketamine and (2R,6R)-HNK were administered either i.p. or locally into the mPFC 24 hr prior measuring swimming duration in the forced swim test (FST) and cortical extracellular 5-HT, GABA, glutamate, glutamine levels in BALB/cJ mouse prefrontal cortex (mPFC).
Results: Systemic (R,S)-ketamine and (2R,6R)-HNK increased swimming duration and mPFC 5-HText. 30min after its systemic administration, (2R,6R)-HNK plasma levels were five times higher than those of (R,S)-ketamine, but both drugs were no longer detected at t24h. Using Zero-net-flux (ZNF) method of quantitative microdialysis, both drugs significantly increased basal Glu release, but did not change its reuptake. Additionally, when perfused locally into the mPFC, both drugs increased swimming duration, (R,S)-ketamine increased mPFC-GABAext, while (2R,6R)-HNK increased mPFC-Gluext.
Conclusions: (2R,6R)-HNK contributes to (R,S)-ketamine sustained antidepressant-like activity. (2R,6R)-HNK and (R,S)-ketamine modify the synaptic excitatory/inhibitory balance by increasing mPFC-glutamate release by pyramidal neurons and GABA release by interneurons, respectively. However, 24h post-administration, when antidepressant and neurochemical effects were observed, (2R,6R)-HNK was absent suggesting that the metabolite has started a cascade of cellular mechanisms.

Supported By: Université Paris-Sud, INSERM
Keywords: Ketamine, (2R,6R)-HNK, Glutamate/GABA, AMPA, Serotonin

189. Developing Single Administration Prophylactics Against Stress-Induced Depression: Ketamine Modifies Memory Traces in the Ventral Hippocampus

Christine Denny

Columbia University

Background: Stress exposure is a major risk factor for mood disorders, such as major depressive disorder and post-traumatic stress disorder. However, some individuals can successfully adapt to stress and this ability is known as stress resilience. We previously reported that a single injection of ketamine prior to stress protects against the development of depressive-like behavior and attenuates learned fear in mice. However, the cellular and molecular pathways underlying ketamine-induced stress resilience are still largely unknown.
Methods: Here, we will discuss ongoing work to identify the mechanisms mediating prophylactic ketamine-induced stress resilience. We utilize a combination of behavioral paradigms, drug development, viral strategies, and the ArcCreERT2 mice, a line that allows for the indelible labeling of neural ensembles representing a single experience.
Results: Prophylactic ketamine protected against the development of stress-induced depressive-like behavior and attenuated fear responses. Prophylactic ketamine administration increased deltaFosB expression in the ventral hippocampus (HPC). In a second set of experiments, mice were stereotaxically injected into ventral CA3 (vCA3) with viral vectors in order to upregulate or downregulate deltaFosB expression before prophylactic ketamine administration. Inhibition of deltaFosB only in vCA3 prevented ketamine's prophylactic effect on fear expression. Current studies are focused on identifying and optogenetically manipulating memory traces following prophylactic ketamine administration.
Conclusions: Overall, these data indicate that prophylactic ketamine may induce protective effects by altering aversive memories, specifically in the ventral HPC. Understanding how prophylactic ketamine may prevent stress-induced depressive-like behavior can elucidate both the pathophysiology of depression and provide insights into potential new treatment targets.
Supported By: NIH DP5, NYSTEM, RISE, Aging Fellowship, Coulter, For the Love of Travis
Keywords: Ketamine, Memory, Hippocampus, deltaFosB, Immediate Early Genes

SYMPOSIUM
Investigating Neurodevelopmental Effects of Stress on Psychiatric Disease in Mice, Monkeys, and Men

12:30 p.m. - 2:30 p.m.
Chair: Christoph Anacker
Co-Chair: Elisabeth Binder

190. Neurogenesis Inhibits Stress-Responsive Cells in the Ventral Dentate Gyrus

Christoph Anacker[1], Victor Luna[2], Gregory Stevens[2], Amira Millette[2], Ryan Shores[2], Briana Chen[2], and Rene Hen[2]

[1]Columbia University, [2]Columbia University & New York State Psychiatric Institute

Background: Adult neurogenesis in the dentate gyrus (DG) of the hippocampus is implicated in behavioral responses to stress and antidepressants. However, how neurogenesis regulates DG information processing to protect from stress-induced behavioral abnormalities is unknown.
Methods: We used in vivo calcium (Ca2+) imaging with miniature microscopes to record Ca2+ activity from large ensembles of DG granule cells in freely moving mice. We imaged DG responses to chronic social defeat stress in wild-type (WT) and in transgenic iBAX mice with a 2±0.2 fold increase in neurogenesis, due to a deletion of the pro-apoptotic gene Bax from adult neural stem cells and their progeny.
Results: On the first day of defeat, no differences in Ca2+ transient rates were observed between WT and iBax mice ($P=0.59$; N=246-460 cells). On the last day of defeat, Ca2+ rates were increased during defeat periods (***$P<0.0001$; N=592-620). iBax mice with increased neurogenesis showed lower Ca2+ responses to defeat stress than WT mice (*$P=0.016$). To assess whether the ventral DG contains heterogeneous cell populations, we used cell selectivity analysis and identified a subset of 34% of neurons that selectively respond to defeat stress. iBAX mice with increased neurogenesis showed lower Ca2+ transient rates than WT mice specifically in the subpopulation of 'stress-selective' cells (***$P<0.0001$; N=169-211). After stress, iBAX mice spent more time interacting in a social interaction test (*$P=0.01$) and more time exploring the center of the open field (*$P=0.04$, N=11-15 mice).
Conclusions: Our results show that neurogenesis inhibits stress-responsive neurons in the ventral DG and confers resilience to chronic stress.
Supported By: K99MH108719-01 (NIMH); Hope for Depression Research Foundation (HDRF); German Research Foundation (DFG)
Keywords: Neurogenesis, Depression, Ventral Hippocampus, Chronic Stress, Calcium Imaging

191. Altered Amygdala Neuroplasticity Systems in Mediating Early Life Anxiety

Ned Kalin

University of Wisconsin School of Medicine and Public Health

Background: Nonhuman primate models of early life anxiety are important in understanding the childhood risk for anxiety and depression. Assessment of molecular alterations in the primate's anxiety circuit can lead to new treatment targets that were tested using viral vector strategies.

Methods: After extensive phenotyping for anxious temperament (AT) in 48 young monkeys, laser capture microdissection techniques are used to collect Ce neurons. RNAseq identified gene expression alterations associated with individual differences in AT. Viral vector methods combined with real time fMRI infusions were used to overexpress NT3.
Results: Results demonstrated alterations in Ce neuronal gene expression that are predictive of individual differences in AT ($p<.05$). Of particular interest was the identification of altered expression of genes that are involved with neuroplasticity and neurotrophism. To causally, test involvement of the TrkC system, we overexpressed the its endogenous ligand, NT3, in the dorsal amygdala of rhesus monkeys. Results demonstrated a reduction in anxiety ($p<.05$) that interestingly was associated with increased metabolism in the amygdala.
Conclusions: These findings suggest that altered neuroplasticity systems in the primate Ce underlie AT. Since AT is an important childhood risk factor for the development of anxiety and depression, these findings suggest a novel intervention target within the Ce. In this regard, we demonstrate that increasing activity of the dorsal amygdala NT3/TrkC in young primates reduces anxiety. These findings have important with implications for the development of novel treatment strategies aimed at reducing the long-term consequences of early-life anxiety.
Supported By: R01MH046729; R01MH081884
Keywords: Anxiety, Amygdala, Childhood, Primate, Neuroplasticity

192. Investigation of Prenatal Stress in the Cerebral Organoid Model: A Focus on Cell-Type Specific Responses Following Glucocorticoid Exposure

Cristiana Cruceanu[1], Simone Roeh[1], Stefanie Wehner[1], Silvia Martinelli[1], Maik Koedel[1], Rossella Di Giaimo[2], Silvia Cappello[1], and Elisabeth Binder[1]

[1]Max-Planck Institute of Psychiatry, [2]Max-Planck Institute of Psychiatry, University of Napoli

Background: The brain undergoes important growth and plasticity during prenatal development, and increased glucocorticoid (GC) exposure is one of the main factors mediating stress effects during this time, likely through epigenetic and transcriptional trajectories. Questions regarding human-specific early neurodevelopmental molecular pathways of prenatal stress cannot be addressed with current animal model tools. Thus, we propose to use iPSC-derived 3-dimensional brain organoids to model prenatally mediated risk and response to stress.
Methods: We performed RNA sequencing (RNAseq) across ten organoid developmental stages (day 17 to 210) to determine this model's suitability. To investigate GC effects in specific cell types, we stimulated organoids with GC-receptor agonist dexamethasone, and profiled 14,000 individual cells' transcriptomes using single cell RNAseq (scRNAseq) across organoid development (days 30, 60, 90).
Results: We identified key neurodevelopment markers expressed in the cerebral organoid model – including SOX2, PAX6, FOXG1, MAP2, with trajectories consistent with increasing neuronal differentiation over time. In a time-course dose-response experiment the combination 100nM dexamethasone over 12 hours was identified as the optimal acute GC-stimulation paradigm as it robustly elicited an effect on GR-regulated gene expression (e.g. FKBP5, FC=4.7). To explore cell type-specific GC response patterns, we used scRNAseq following dexamethasone treatment. We found dynamic expression of genes associated with GC-responsive pathways with differential response in specialized brain cells.
Conclusions: Cerebral organoids follow developmental trajectories of the human brain and show responsiveness to glucocorticoids consistent with in vivo data, including cell-type specific responses. The identified pathways may shed light on risk genes moderating the effects of prenatal stress in humans.
Supported By: Alexander von Humboldt Foundation, Max Planck Society
Keywords: Prenatal Stress, Cerebral Organoids, Glucocorticoids, Single Cell Type Sequencing

193. Sex Specific Effects of Maternal Cortisol Concentrations During Pregnancy on the Functional Connectivity of the Newborn Limbic System

Alice Graham[1], Jerod Rasmussen[2], Sonja Entringer[3], Marc Rudolph[1], Martin Styner[4], John Gilmore[4], Pathik Wadhwa[2], Damien Fair[1], and **Claudia Buss**[3]

[1]Oregon Health and Science University, [2]UC Irvine, [3]Charite University Medical Center Berlin, [4]University of North Carolina at Chapel Hill

Background: Identifying prenatal influences on the rapidly developing fetal brain is important for understanding the etiology of psychiatric disorders and sex differences in their prevalence. We examined sex-specific associations between maternal cortisol concentrations throughout pregnancy, coordinated functioning of the amygdala in neonates, and emerging internalizing symptoms when children were 24-months-of-age.
Methods: The data were collected in the context of an ongoing prospective longitudinal study of maternal-fetal/infant-dyads (N=70 infants; 32 females). Average maternal cortisol output during pregnancy was estimated as mean area under the curve (AUC) derived from 5-daily saliva samples on 4-days in each trimester. Resting state functional connectivity MRI was examined in neonates using individually segmented amygdala seeds.
Results: Significant interactions between maternal cortisol and infant sex were identified for the functional connectivity of the neonatal amygdala ($p<0.05$ with monte carlo simulation for multiple comparisons correction). For females, higher maternal cortisol was associated with increased amygdala connectivity to brain regions involved in sensory processing and integration, including the supramarginal gyrus (SMG) extending into posterior insula. In contrast, for males, higher maternal cortisol concentrations were associated with weaker amygdala connectivity to sensory processing regions. These patterns of neonatal amygdala connectivity were in turn associated with internalizing symptoms at 24-months-of-age.

Conclusions: The distinct pattern of integrating versus segregating the amygdala from sensory processing and integration regions may reflect unique strategies for males versus females in adapting to a stressful environment signaled by heightened maternal cortisol during pregnancy. These neural phenotypes appear to have implications for emerging internalizing behavior, such that females are at heightened risk.
Supported By: NICHD R01 HD060628, NIMH R01 MH091351
Keywords: Developmental Programming, Pregnancy, Human Brain Development, Resting State Functional Connectivity, Cortisol

SYMPOSIUM
Lipids and White Matter Abnormalities in Psychiatric Illness: Biomarkers, Mechanisms, and Preclinical Modeling

12:30 p.m. - 2:30 p.m.
Chair: M. Elizabeth Sublette
Co-Chair: Bart Peters

194. Deficits in Docosahexaenoic Acid Accrual During Adolescence Reduce Rat Forebrain White Matter Microstructural Integrity: An in vivo Diffusion Tensor Imaging Study

Robert McNamara[1], Jennifer Schurdak[1], Ruth Asch[1], and Diana Lindquist[2]

[1]University of Cincinnati College of Medicine, [2]Cincinnati Children's Hospital Medical Center

Background: Neuropsychiatric disorders that frequently initially emerge during adolescence may be associated with deficits in the omega-3 fatty acid docosahexaenoic acid (DHA), elevated pro-inflammatory signaling, and regional reductions in white matter integrity (WMI). The present study determined the effects of altering brain DHA accrual during adolescence on WMI in rat brain by diffusion tensor imaging (DTI), and investigated the potential mediating role of pro-inflammatory signaling.
Methods: During peri-adolescent development male rats were fed a diet deficient in omega-3 fatty acids (DEF, n=20), a fish oil-fortified diet containing preformed DHA (FO, n=20), or a control diet (CON, n=20). In adulthood, DTI scans were performed and brain WMI analyzed using voxelwise tract-based spatial statistics ($p \leq 0.05$ corrected). Postmortem fatty acid composition, peripheral (IL-1beta, IL-6, CRP) and central (IL-1beta, CD11b) pro-inflammatory markers were determined.
Results: Compared with CON rats, forebrain DHA levels were lower in DEF rats (-30%, $p \leq 0.0001$) and higher in FO rats (+8%, p=0.01). Compared with CON rats, DEF rats exhibited greater radial diffusivity (RD) and mean diffusivity (MD) in the right external capsule, and greater axial diffusivity (AD) in the corpus callosum genu and left external capsule. DEF rats also exhibited greater RD in the right external capsule compared with FO rats. There were no group differences for fractional anisotropy. Central (IL-1beta) and peripheral (IL-1beta, IL-6) pro-inflammatory markers were lower in FO rats but were not significantly elevated in DEF rats.
Conclusions: These findings demonstrate that deficits in adolescent DHA accrual negatively impact forebrain WMI independent of elevated pro-inflammatory signaling.
Supported By: Supported in part by National Institute of Health grants MH107378, DK097599, and MH097818
Keywords: Omega-3 Fatty Acids, Neuroinflammation, Diffusion Tensor Imaging (DTI), Adolescence, White Matter Tractography

195. Fatty Acid Bioavailability and Membrane Dynamics are Associated With White Matter Integrity and Neurocognitive Performance During Development

Bart Peters[1], Philip Szeszko[2], Robert McNamara[3], Aristotle Voineskos[4], Tristram Lett[4], Pamela DeRosse[5], Saurav Guha[6], Katherine Karlsgodt[7], Toshikazu Ikuta[8], Daniel Felsky[9], Majnu John[5], David Rotenberg[10], Todd Lencz[6], Anil Malhotra[6], Arne Popma[11], and Tanja Vrijkotte[12]

[1]VU University Medical Center; Arkin Youth & Family, [2]Icahn School of Medicine at Mount Sinai, [3]University of Cincinnati College of Medicine, [4]University of Toronto and Centre for Addiction and Mental Health, [5]Feinstein Institute for Medical Research, [6]Zucker Hillside Hospital, [7]UCLA, [8]University of Mississippi, [9]Brigham and Women's Hospital, Harvard Medical School, Broad Institute, [10]Centre for Addiction and Mental Health, [11]Free University (VU) Medical Center, [12]Academic Medical Center

Background: Psychiatric disorders are associated with polyunsaturated fatty acid (PUFA) abnormalities and altered brain white matter (WM) integrity. We investigated the effect of PUFA bioavailability and membrane dynamics, in utero and childhood, on brain WM integrity and neurocognitive performance across childhood development.
Methods: In a birth-cohort (Amsterdam Born Children and their Development), prenatal maternal PUFA concentrations (phospholipid-associated fatty acids in week 13) were assessed, and neurocognitive performance tested in the child offspring at age 5-6 years (n=921).

In addition, we examined a fatty acid desaturase (FADS) gene haplotype, which regulates PUFA biosynthesis, in relation to WM development cross-sectionally in healthy individuals aged 9-86 years (n=205) using diffusion tensor tractography. We also examined plasma activity of phospholipase A2 (PLA2), an enzyme which regulates PUFA release and turnover in phospholipid membranes, and WM integrity in healthy individuals aged 9-19 years (n=29).
Results: Prenatal docosahexaenoic acid (DHA) plasma concentration was associated with child visuomotor coordination accuracy (p=.029) and accuracy stability (p=.045). Prenatal docosapentaenoic acid was associated with child baseline speed (p=0.049) and speed stability (p=0.029), independent of age and sex. Individuals homozygous for the FADS minor allele (associated with lower DHA concentrations) lacked normal age-related WM differences across childhood, compared to major allele carriers (age-by-genotype interaction; $p < 0.0001$).

PLA2 activity showed a significant U-curved association with WM radial diffusivity (p=0.036), independent of age.
Conclusions: Our data suggest that PUFA bioavailability in utero is important to childhood neurocognitive development, which may be mediated by effects of PUFA biosynthesis and membrane dynamics on brain WM development.
Supported By: Grant R01 MH076995 (P.R. Szeszko), Grant R01 MH099167 (A.N. Voineskos), Grant M01 RR018535 to the North Shore-Long Island Jewish Health System, Grant P30 MH090590, Grant P50 MH080173 (A. Malhotra) , Canadian Institutes of Health Research (A.N.V.), Dana Foundation (P.R.S.), Brain and Behavior Research Foundation (A.N.V.), Ontario Mental Health Foundation (A.N.V.), CAMH, and the CAMH Foundation, thanks to the Kimel Family, Koerner New Scientist Award, and Paul E. Garfinkel New Investigator Catalyst Award., Grant DK097599 (Dr. McNamara), NARSAD grant from the Brain and Behavior Research Foundation to Dr. Peters
Keywords: Diffusion Tensor Imaging (DTI), White Matter Microstructure, Brain Development, Children and Adolescence, N-3 Polyunsaturated Fatty Acids

196. Polyunsaturated Fatty Acid Supplementation is Related to White Matter Integrity and Glucose Uptake in Major Depressive Disorder

M. Elizabeth Sublette[1], Francesca Zanderigo[2], Harry Rubin-Falcone[2], Maria Oquendo[3], and J. John Mann[2]

[1]Columbia University, [2]New York State Psychiatric Institute, Columbia University Medical Center, [3]University of Pennsylvania

Background: We have previously reported that six weeks of open-label omega-3 polyunsaturated fatty acid (PUFA) supplementation in depressed patients (MDD, n=16) and healthy volunteers (HV, n=12) resulted in symptom improvement and reduced regional group differences in fractional anisotropy (FA). Clinical improvement correlated with endpoint docosahexaenoic acid as a percentage of plasma phospholipid PUFAs (DHA%) and predicted increased FA, while increased endpoint DHA% predicted FA increases in MDD, FWE-corrected. Brain regions where increased FA correlated with improved depression and increased DHA% overlapped. We next sought to relate WM integrity with WM metabolic functioning.
Methods: In the same cohort, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 14 MDD and 7 HV before and after supplementation. Venous samples were taken at 40 min post-injection and FDG cerebral metabolic rate of glucose (rCMRglu) calculated for total WM and gray matter (GM) using the simultaneous estimation of input function method.
Results: We observed baseline differences in FDG uptake between diagnostic groups in GM (p=0.050) and WM (p=0.025) that resolved after supplementation. Change in DHA % after supplementation predicted final rCMRglu (GM, p=0.016; WM, p=0.017) controlling for age. However, rCMRglu in WM was not related to DTI FA levels (in regions of FA-DHA% correlation) either pre- (p=0.709) or post- (p=0.922) supplementation. In MDD, WM rCMRglu after supplementation trended toward positive correlation with depression scores, controlling for baseline rCMRglu (p=0.099).
Conclusions: Our results suggest that clinical improvement after omega-3 PUFA supplementation is related to both altered WM integrity and metabolism. However, different pathways may be involved as these bioindices did not evince a direct interrelationship.
Supported By: This work was funded by K-08 MH079033 (PI:Sublette) and R01 MH48514 (PI:Oquendo). Omega-3 PUFA supplements were donated by Unicity, International, Inc. (Orem, UT, USA)
Keywords: Omega-3 Fatty Acids, Depression, White Matter, 18FDG PET, Diffusion Tensor Imaging (DTI)

197. Omega-3 Polyunsaturated Fatty Acids May Protect Against White Matter Abnormalities Found in Early Phase Psychosis

Philip Szeszko[1], Amanda Lyall[2], Marek Kubicki[2], Juan Gallego[3], Anil Malhotra[4], Ofer Pasternak[2], Lauren Hanna[4], Robert McNamara[5], Delbert Robinson[4], and Bart Peters[6]

[1]Icahn School of Medicine at Mount Sinai, [2]Brigham and Women's Hospital, Harvard Medical School, [3]Weill Cornell Medical College, [4]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, [5]University of Cincinnati College of Medicine, [6]VU Medical Center

Background: White matter (WM) abnormalities play a role in the pathogenesis of psychosis that may, in part, be related to antipsychotic treatment. Omega-3 polyunsaturated fatty acids are constituents of the myelin sheath formed from membranes of oligodendrocytes. We investigated the relationship between omega-3 supplementation of antipsychotic treatment and WM changes in psychosis.
Methods: Thirty-nine (30M/9F) patients with diffusion tensor imaging (DTI) scans were recruited from a larger clinical trial and randomized to treatment with either risperidone+omega-3 [i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] or risperidone+placebo for 16 weeks. Nineteen patients had follow-up scans available for analysis (N=9 risperidone+placebo and N=10 risperidone+omega-3). We used free-water-imaging (FWI) to separate the extracellular space (potentially reflecting an immune-related response) from neuronal tissue changes to compute an extracellular FWI map, fractional anisotropy (FA) of the tissue (FA-t) map and traditional FA map that were projected onto a white matter "skeleton" using Tract-Based Spatial Statistics.
Results: Significant (p<.05) positive correlations were identified between erythrocyte omega-3 index (i.e., EPA+DHA) and average FA and FA-t prior to treatment across the entire sample. The omega-3 index increased significantly (p<.05) among individuals treated with risperidone+omega-3 compared to patients treated with risperidone+placebo. Patients treated with risperidone+placebo demonstrated significant reductions in FA and FA-t and a significant (p<.05)

increase in FWI across the 16-week trial. In contrast, no significant (p>.05) changes in these measures were evident among patients treated with risperidone+omega-3.
Conclusions: Our findings suggest that omega-3 supplementation of risperidone may mitigate WM changes associated with antipsychotic treatment.
Supported By: NIMH
Keywords: Omega 3, Diffusion Tensor Imaging (DTI), Early Psychosis, Antipsychotic

SYMPOSIUM
Computational Neuroscience Approaches to Understanding the Onset and Neurobiology of Youth Depression

12:30 p.m. - 2:30 p.m.
Chair: Christopher Davey
Co-Chair: Lianne Schmaal

198. Identifying Structural Brain Alterations in Adolescent Depression Based on Individual Deviations From Normative Age-Related Patterns of Brain Structure

Lianne Schmaal[1], Yara Toenders[1], Paul Thompson[2], Dick Veltman[3], and Andre Marquand[4]

[1]Orygen, The National Centre of Excellence for Youth Mental Health, [2]Keck School of Medicine of University of Southern California, [3]VU University Medical Center, [4]Radboud University

Background: Recent studies have suggested that major depressive disorder (MDD) may dynamically affect the brain depending on stage of life. Identifying structural brain alterations as individual deviations from normative patterns of brain development may provide insights into these dynamic and heterogeneous patterns of brain abnormalities observed in adolescent MDD.
Methods: Structural brain measures derived using FreeSurfer from 32 research samples participating in the ENIGMA MDD consortium were pooled. Normative models mapping the association between age and structural brain measures were estimated in 4,708 healthy controls using Gaussian Process Regression. These models were applied to 1,124 MDD patients (aged 12-30) to obtain predicted brain values for each patient based on their age. Z-scores quantifying the difference between predictive and true brain values measures were calculated and associated with clinical characteristics.
Results: Various subsets of patients with greater as well as smaller cortical thickness, surface area and subcortical volumes than predicted from the normative models were identified (Z<-1 and Z>1). For example, one subset of patients showed thinner frontal, temporal and cingulate regions and was characterized by a higher percentage of recurrent episodes, fewer people on antidepressant medication and older age compared to patients residing within the normative range (all P<0.01).
Conclusions: The normative modeling approach we applied here provides a framework to study adolescent depression at the individual level and to consider brain alterations as deviations from normal brain development. Our results show that when considering individual deviations instead of group-averages, the picture of structural brain alterations in adolescent depression appears much more complex.
Supported By: NIH Big Data to Knowledge (BD2K) award (U54 EB020403)
Keywords: Adolescent Depression, Structural MRI, Big Data, Age-Related Deviations

199. Girls' Childhood Relationships, Adolescent Reward Circuitry, and Depression: A Prospective, Longitudinal Study

Erika Forbes[1], Neil Jones[2], Gabriela Alarcon[1], Amanda Guyer[3], Kathryn Keenan[4], and Alison Hipwell[1]

[1]University of Pittsburgh, [2]University of Pittsburgh School of Medicine, [3]University of California, Davis, [4]University of Chicago

Background: Challenging family contexts are a potent influence on brain development, with consequences for depression. Family relationship factors—for example, low mother-child relationship quality or low warmth— are especially associated with function in neural reward systems. Using detailed social-context measures and fMRI in a prospective longitudinal study of high-risk girls, this presentation will examine neural response to reward as a mechanism of associations between early adversity and adolescent depression.
Methods: Participants were 232 adolescent girls followed from age 5-19 as part of a community study of risk for depression. Mothers completed measures of parenting practices, parent-child relationship quality, parent-partner conflict, family climate, and maltreatment at ages 5-10. Girls completed diagnostic interviews at ages 9-18 and underwent fMRI on a Trio 3T scanner with a monetary reward task at 16, 17, 18, and 19 years. Analyses were conducted in AFNI. Multiple testing was addressed with family-wise error correction at p<.05, and the PROCESS macro was used to test mediation.
Results: Exploratory factor analyses yielded 3 childhood relationship factors: relationship quality, maternal involvement, and rewarding desired behavior. Relationship quality predicted age 16 mid-cingulate response to reward, rewarding behavior predicted age 16 putamen response, and superior temporal gyrus response mediated associations between rewarding behavior at age 5 and depression at age 16. From age 16-17 increasing depression was associated with increasing dorsolateral prefrontal cortex response.
Conclusions: Neural reward systems could be sensitive to early social-context influences, particularly in the family domain. Disruption of development in these systems could provide a mechanism for higher vulnerability to depression.
Supported By: NIMH R01
Keywords: Adolescent Depression, Reward Circuitry, Psychosocial Stress, Parenting

200. Differing Windows of Sensitivity to Stress in Amygdala-Ventromedial Prefrontal Cortex Structural and Functional Connectivity: Implications for the Neurobiology of Depression in Youth

Tiffany Ho[1], Kathryn Humphreys[1], Lucy King[1], Natalie Colich[1], Jaclyn Schwartz[1], Josiah Leong[1], Kyoko Ohashi[2], Martin Teicher[3], and Ian Gotlib[1]

[1]Stanford University, [2]McLean Hospital, [3]McLean Hospital, Harvard Medical School

Background: Early life stress (ELS) affects the development of structural (SC) and functional connections (FC) between amygdala and ventromedial prefrontal cortex (vmPFC), a stress regulatory circuit that matures throughout adolescence and is implicated in the onset of depression in youth. It is unclear, however, whether stress sensitive periods differ for FC and SC, and what are the effects of each on adolescent depression.
Methods: We conducted structured interviews to record timing and severity of ELS and collected diffusion MRI and resting-state fMRI in a community sample of 127 adolescents (age range: 11-15 years; mean±SD: 12.76±1.13 years; 64 females). We applied random forest regression with conditional inference trees to identify stress sensitive periods (i.e., ages at which maximum severity of stress exposure had the strongest predictive effect) of amygdala−vmPFC connectivity. We used linear regression to examine associations between self-report depression scores and amygdala−vmPFC FC and SC.
Results: Amygdala−vmPFC SC exhibited an earlier peak of stress sensitivity (left: age 6, p=0.039; right: age 7, p=0.052). Left FC sensitivity occurred relatively later (age 9, p=0.034); however, right FC exhibited no significant stress sensitivity period. Only left SC and FC were significantly intercorrelated (B=2.01±0.71, t74=2.83, p=0.006). Finally, only left FC was associated with depressive symptoms (B=74.90±35.63, t123=2.10, p=0.038).
Conclusions: The window of sensitivity to stress may be left-lateralized and occur first in amygdala−vmPFC SC, which then influences FC. Future longitudinal work is needed to assess effects of ELS timing on amygdala−vmPFC SC and FC development and, in turn, the effects of each on emergence of depression.
Supported By: R01MH101495; K01MH106805; Klingenstein Third Generation Foundation
Keywords: Adolescence, Major Depressive Disorder (MDD), Early Life Stress, Diffusion Tensor Imaging (DTI), Resting State fMRI

201. A Dynamic Causal Model of the Depressed Self

Christopher Davey[1], Michael Breakspear[2], Jesus Pujol[3], and Ben Harrison[1]

[1]University of Melbourne, [2]Queensland Institute of Medical Research, [3]Hospital Del Mar, Barcelona

Background: A disturbed sense of self is a core feature of depression. The medial prefrontal cortex, which has a central role in self-appraisal processes, is often implicated in the illness, although it remains unclear how functional alterations of the region contribute to the observed disturbances. The aim of this study was to clarify the role of the medial prefrontal cortex in self-appraisal processes in depression.
Methods: We applied a recently developed dynamic network model of self-directed cognition to functional MRI data from 71 adolescents and young adults with moderate to severe major depressive disorder, none of whom were being treated with medication, and 88 healthy control participants. Bayesian model averaging was used to determine parameter estimates for the dynamic causal models, which were compared between groups.
Results: While self-directed cognitive processes in the depression group were shown to rely on the same dynamic network as in the healthy control group, the medial prefrontal cortex had a "hyperregulatory" effect on the posterior cingulate cortex in the depressed group, with self-appraisal causing significantly more negative modulation of connectivity between the medial prefrontal cortex and the posterior cingulate cortex than in the control group (odds ratio=0.54, 95% CI=0.38, 0.77). This parameter was significantly inversely related with a depression factor related to poor concentration and inner tension (r=20.32; 95% CI=20.51, 20.08).
Conclusions: The exaggerated influence of the medial prefrontal cortex on the posterior cingulate cortex in depression is a neural correlate of the disturbed self-appraisal that is characteristic of the illness.
Supported By: NHMRC (Australia)
Keywords: Depression, fMRI, Dynamic Causal Modeling, Youth, Self-Reflection

SYMPOSIUM
The Promise of Deep Learning for Psychiatry
12:30 p.m. - 2:30 p.m.
Chair: Guido van Wingen

202. Deep Learning Technology: Concepts and Applications in Biological Psychiatry

Andrea Mechelli[1]

[1]Institute of Psychiatry, Psychology & Neuroscience, King's College London

Background: Technology companies such as Google, Facebook and Apple have long been using deep learning technology (DLT) for big data analysis in order to predict how people search the internet and what news they are interested in. In light of its superior ability to detect high orders of complexity and abstraction in the data, DLT is now becoming the focus of increasing attention in the brain sciences. This presentation will provide an overview of DLT and its potential applications to the investigation of brain-based disorders. In the first part of the presentation, I will outline the key concepts of DLT. One of the simplest DLT structures, the multilayer perceptron, will be used to illustrate the steps of training and testing. In the second part of the presentation, I will discuss potential applications of DLT in biological psychiatry. To illustrate one of these applications,

I will present a novel investigation that compared the performance of DLT against that of shallow machine learning methods.
Methods: A type of DLT known as Convolutional Neural Network and three shallow machine learning methods (Support Vector Machine, Multi-Kernel Learning and Logistic Regression) were applied to five independent multi-modal neuroimaging datasets comprising 295 patients with psychosis and 452 healthy controls.
Results: DLT was able to detect patients and controls with a balanced accuracy of 78% ($p<0.001$); this was superior to the performance of shallow machine learning methods which was in the 70%-72% range.
Conclusions: SVM has the potential of becoming a powerful tool in the search for biomarkers of psychiatric disorders.
Supported By: The Wellcome Trust
Keywords: Machine Learning, Deep Learning Technology, Psychosis, Neuroimaging

203. Decoding the Role of Noncoding Genome in Neurological Disease With Deep Learning

Jian Zhou[1], Chandra Theesfeld[2], and Olga Troyanskaya[3]

[1]Flatiron Institute, Simons Foundation, [2]Princeton University, [3]Princeton University & Flatiron Institute of the Simons Foundation

Background: A key challenge in psychiatry and medicine in general is to develop a complete understanding of the genomic architecture of disease. Yet the generation of WGS data has not been matched by a way to interpret the 98% of the noncoding genome. This is because we do not know how to interpret noncoding variants at scale, and, importantly, how significant such noncoding variants will be for clinical insight.
Methods: We developed an innovative deep learning approach that directly learns the regulatory code from large-scale chromatin- and transcription factor-profiling data to enabling de novo prediction of regulatory effects of sequence alterations with single-nucleotide sensitivity. We demonstrate its value by focusing on the causal contribution of noncoding variants to clinical outcomes in autism spectrum disorder (ASD). Even relatively sophisticated traditional analyses fail to find such signals because many noncoding mutations aren't functional and there are enormous statistical challenges in such studies.
Results: In contrast, our deep learning method allow us to interpret the noncoding regulatory code in a way parallel to the genetic code, predicting functional impact of genetic variants on regulation. This enables systematic interpretation of whole genome data from a large ASD cohort of 540 families, yielding quantitative predictions of the regulatory impact of tens of thousands of noncoding mutations and the consequent clinical interpretations. We pinpoint specific transcriptional regulatory-disrupting mutations as causal to the etiology of autism.
Conclusions: This work also highlights the clinical importance of WGS and identifies the first systematic association of noncoding regulatory mutations with clinical outcomes in ASD.
Supported By: NIH RO1, Simons Foundation
Keywords: Autism, Autism Spectrum Disorder, Deep Learning Technology, Genetics, Whole Genome Sequencing

204. Exploring Deep Learning for Various rsfMRI Summary Measures

Rajat Thomas[1], Guido van Wingen[1], and Paul Zhutovsky[1]

[1]University of Amsterdam Academic Medical Center

Background: Deep learning technology (DLT) has been successfully applied to structural MRI scans in neurology and psychiatry to classify patients from controls. In this study, we set out to explore the potential of resting state functional MRI (rsfMRI) because, especially for psychiatric disorders, the abnormalities are often manifested in the temporal activity of various brain regions. But, unlike MRI, rsfMRI is extremely high-dimensional to be used as input to conventional deep learning algorithms. Therefore, we explored measures to summarize the time-course voxelwise to reduce the dimensions. These measures include entropy, power, local network properties and auto correlation lags.
Methods: To facilitate future comparisons, we used the data from ABIDE preprocessed CPAC pipeline. The DLT was implemented in Tensorflow (Google) and the architecture consisted of four convolutional and three fully-connected layers. No additional processing was done on the data.
Results: ABIDE data set consisted of 884 (controls =406, ASD=406) subjects. Local functional connectivity density metric provided the highest classification accuracy (balanced) of 63%. Other measures were similar. But combining all measures resulted in a 70% accuracy; highest reported accuracy in classifying controls vs ASD in the ABIDE data set.
Conclusions: DLT applied to multi-modal neuroimaging is a promising avenue to explore. Once trained, the models are extremely light-weight and can be embedded on current imaging systems. We envision a future in which psychiatrists are regularly assisted by DLT for informed decision making on the diagnosis and treatment planning in psychiatric disorders.
Supported By: NWO
Keywords: Deep Learning Technology, Resting State fMRI, Neuroimaging

205. Deep Learning Approaches to Unimodal and Multimodal Analysis of Brain Imaging Data With Applications to Mental Illness

Vince Calhoun[1] and Sergey Plis[2]

[1]The University of New Mexico, [2]Mind Research Network

Background: Deep learning analytic approaches have made inroads into the brain imaging field, but they are still relatively new and the specific applications which can benefit from such models are not yet fully developed. In this talk I will present some work in which we have developed deep learning models with application to structural and functional brain imaging data in mental illness including schizophrenia, bipolar disorder, and Huntington's disease.
Methods: We apply and discuss several recent deep learning models which were developed for application to brain imaging data. The first model is focused on structural MRI data, the

second on fMRI data, and the third on functional and structural data integration. We then demonstrate performance of these models on several multi-site studies of schizophrenia, bipolar disorder, and Huntington's disease.
Results: Results provide strong evidence for the potential of deep learning and motivate its future use. In particular, deep models outperformed single layered models in terms of differentiating patient and control group and capturing disease severity measures. These models also demonstrate the ability of deep learning to help us better understand patients who fall on the boundary between diagnostic categories. And finally, results show the relationship between brain structure and function is disrupted in schizophrenia, especially in networks involving temporal lobe and insular brain regions.
Conclusions: Deep learning involves more complex models, which one might think would be something to be avoided. However current evidence supports the need for such models to help unravel the complex relationship between mental illness and brain function and structure.
Supported By: P20GM103472; 2R01EB005846; NSF 1539067
Keywords: Deep Learning, Schizophrenia, Brain Imaging, Structural, Functional

SYMPOSIUM
Time is of the Essence: Temporal Macro- and Micro-Architecture in Psychiatric Disorders
12:30 p.m. - 2:30 p.m.
Chair: Hilary Blumberg
Co-Chair: Philip Shaw

206. Neuroimaging View of the Temporal Architecture of Bipolar Disorder

Elizabeth Lippard[1], Siyan Fan[2], Judah Weathers[2], Fei Wang[2], and **Hilary Blumberg**[2]

[1]UT Austin, [2]Yale School of Medicine

Background: Characteristics of bipolar disorder (BD) are dynamic changes in symptoms and behaviors from macro to micro temporal levels. At the macro level, for at least a large subset of individuals, BD appears to be a neurodevelopmental disorder with critical periods including adolescence and young adulthood. In adulthood, subsets of individuals with BD have also been recognized to show progression of symptom subsets. Recurrence of acute mood symptoms occurs at rates of years to weeks, and in some instances shorter durations. This talk will include data demonstrating neural circuitry correlates of these time-related changes in BD. Additionally, rapid and longer term salutary effects on brain circuitry, symptoms and behaviors of a novel psychobehavioral treatment to improve emotional regulation will be presented.
Methods: Anatomical, functional and diffusion-weighted magnetic resonance imaging, symptom and behavioral data will be presented from cohorts of >300 individuals each in BD or healthy comparison (HC) groups, ages 10-80 years for whom a subset longitudinal neuroimaging data (rescanned on average about 2.5 years) was also obtained.
Results: New findings presented will include significant (p-values at least <0.05 for region of interest models or 0.005 for voxel-based analyses) BD vs. HC differences in age- and time-related changes over the 10-80 year age span, within BD related to mood state changes and cycling rate, as well as rapid and sustained changes in response to the psychobehavioral intervention.
Conclusions: Discussion will include implications for elucidating pathophysiology in BD of developmental, aging and acute-episode generating processes, and for differential diagnosis, early detection, treatment and prevention strategies.
Supported By: NIMH, BBRF, IBF AFSP
Keywords: Bipolar Disorder, Brain Development and Aging, MRI Brain Imaging

207. From Milliseconds to Years in Attention Deficit Hyperactivity Disorder

Philip Shaw[1] and Gustavo Sudre[2]

[1]NHGRI/NIMH, [2]NHGRI

Background: We consider how mapping neural activity in the order of milliseconds (the temporal microscale) can throw insights into processes pertinent to attention deficit hyperactivity disorder that have unfolded over years (the temporal macroscale). Specifically, we demonstrate how the degree of persistence into adulthood of childhood symptoms of inattention and hyperactivity/impulsivity is associated with patterns of adult neural activity.
Methods: 220 children had the course of their symptoms of inattention and hyperactivity/impulsivity assessed repeatedly into early adulthood. In adulthood, all had multimodal imaging (fMRI and magnetoencephalography- MEG) during both task of response inhibition and task free processing.
Results: The severity of symptoms persisting from childhood were tied to anomalies in functional connectivity, defined both electrophysiologically (using MEG) and hemodynamically (using fMRI), during task free and task dependent processing. All reported symptom-function associations reported survived adjustment for multiple testing through false discovery or Bonferroni procedures (adjusted alpha of 0.05). Adults whose symptoms had remitted showed neural activation patterns that did not differ significantly from individuals who were never affected. By contrast, adults with persistent symptoms differed significantly from those never affected, particularly in brain regions supporting response inhibition, and in the connectivity between the default mode network and networks supporting attention.
Conclusions: We find that adults whose ADHD symptoms have resolved since childhood do not differ from their never-affected peers both neuro-electrophysiologically and hemodynamically. This is compatible with a model that holds remission occurring over year might be underpinned by a normalization of early anomalies of cortical dysfunction.
Supported By: Intramural NHGRI and NIMH
Keywords: ADHD, Remission, Multimodal Neuroimaging

208. Behavioral and Neural Sustained Attention Deficits in Bipolar Disorder and Familial Risk of Bipolar Disorder

David Pagliaccio[1], Jillian Wiggins[2], Nancy Adleman[3], Elizabeth Harkins[4], Alexa Curhan[4], Kenneth Towbin[5], Melissa A. Brotman[5], Daniel S. Pine[5], and Ellen Leibenluft[5]

[1]Columbia-NYSPI, [2]San Diego State University, [3]The Catholic University of America, [4]NIMH, [5]National Institute of Mental Health, National Institutes of Health

Background: Few neuroimaging studies compare individuals affected with bipolar disorder (BP), at high familial risk of BP, and at low risk to identify endophenotypes for BP. None have examined millisecond scale variability in trial-by-trial deployment of attention, despite promising behavioral work.
Methods: The present study examined 8- to 25-year-old individuals (n=106) who completed an fMRI attention task: 24 with BP, 29 at risk based on a first-degree relative with BP, and 53 healthy, low-risk individuals. Group differences in intra-subject variability in reaction time were examined, and trial-wise associations between reaction time and brain activity were quantified.
Results: Relative to healthy individuals, those with BP or at risk exhibited increased reaction time variability ($F_{2,102}=4.26$, $p=.02$, $\eta p2=.08$). Importantly, we identified blunted relationships between trialwise variation in reaction time and brain activity in the inferior and middle frontal gyri, precuneus, cingulate cortex, caudate, and postcentral gyrus (all regions: $p<.001$, $\eta p2>.06$) in both at-risk and BP individuals compared with healthy, low-risk individuals. This blunting partially mediated group differences in reaction time variability ($\beta=.010$, 95% confidence interval 0.002 to 0.020, Sobel $Z=2.08$, $p=.038$).
Conclusions: Blunting in key frontal, cingulate, and striatal areas was evident in unaffected, at-risk individuals and in euthymic BP patients. Elucidating such novel neural endophenotypes can facilitate new approaches to BP prediction, diagnosis, and prevention. Additionally, the results suggest that examining the temporal microstructure of brain-behavior relationships may be critical to understanding risk for BP.
Supported By: NIH intramural research program
Keywords: Bipolar Disorder, BOLD fMRI, Attention

209. Cognitive and Neuroimaging Approaches to Uncovering the Temporal Architecture of ADHD

Sarah Durston[1], Sara Ambrosino[1], Janna van Belle[1], and Branko van Hulst[1]

[1]Brain Centre Rudolf Magnus, University Medical Centre Utrecht

Background: Temporal dynamics are particularly relevant to ADHD, at both the Micro- and the Macro-level. At the Micro-level, the most robust finding for cognitive changes in ADHD is for moment-to-moment variability in response timing on cognitive tasks, whereas at the Macro-level, changes in brain structure with development have been tied to clinically relevant measures, such as outcome and stimulus treatment. I will consider how individual differences in reactivity in ADHD and ASD (micro-level) and longitudinal data on the temporal dynamics of development (macro-level) may inform us on underlying psychopathological mechanisms.
Methods: Cognitive data were collected from 405 children with ADHD, ASD & TD. Ex-Gaussian distribution parameters were used to characterize intra-individual variability on fast and slow responses. Longitudinal measures of brain development were collected for children with ADHD and controls.
Results: We found higher variability on both fast and slow responses for children with ADHD and ASD ($p < .05$). For children with ASD, variability remained high over development, whereas for children with ADHD it decreased at a rate similar to controls. Similarly, we found widespread reductions in cortical surface area and gyrification in ADHD that were stable over development ($p < .05$).
Conclusions: I will discuss how differences in response variability give insights into shared and unique mechanisms across ADHD and ASD. Additionally, I consider how measures of brain anatomy can inform us on early developmental mechanisms. These findings will be contrasted to those on mood disorders also discussed in the symposium.
Supported By: Dutch Science Foundation (NWO) VENI 451-02-108, VIDI 917.76.384 & VICI 453-10-005
Keywords: ADHD, Cortex, Reaction Time Variability

SYMPOSIUM
The Gut Microbiome-Brain Connection: Implications for Neurodevelopment and Psychiatric Disorders

12:30 p.m. - 2:30 p.m.
Chair: Aleksandra Vicentic
Co-Chair: Nancy Desmond

210. Microbiome & the Brain in Mental Illness: Moving Towards Mechanisms & Medicines

Gerard Clarke[1] and John Cryan[1]

[1]University College Cork

Background: There is a growing realization that the gut-brain axis and its regulation by the microbiota may play a key role in the biological and physiological basis of neurodevelopmental, age-related and neurodegenerative disorders. Dr. Clarke will open the symposium by summarizing the evidence linking the microbiome to fundamental aspects of brain function and behavior.
Methods: Strategies used to parse the role of microbiota in brain function include germ free animals, antibiotic treatments, dietary manipulations, probiotics and prebiotics. Fecal microbiota transplants allow the moving from correlation to causation. Finally, human studies are ongoing to translate such findings.
Results: The microbiome has been linked to fundamental aspects of brain function across the lifespan including myelination, synaptic plasticity, neurogenesis and neuroimmune function. The routes of communication between the microbiota and brain are being unravelled and include the vagus nerve, gut hormone signalling, the immune system, tryptophan metabolism or by way of microbial metabolites such as short

chain fatty acids. The importance of early life gut microbiota in shaping future health outcomes is also emerging. Disturbances of this composition by way of antibiotic exposure, lack of breastfeeding, infection, stress and the environmental influences coupled with the influence of host genetics can result in long-term effects on physiology and behavior, at least in animal models.
Conclusions: It is plausible that by selective targeting of the microbiota may lead to a psychobiotic approach to treating mental illness in the future.
Supported By: Science Foundation Ireland SFI/12/RC/2273; NARSAD 20771
Keywords: Chronic Stress, Gut Microbiome, Gut Microbiota, Commensal Gut Bacteria, Psychobiotics

211. Prenatal Stress Leads to Sex-Specific Changes in Behavior, Inflammation, and Serotonergic Dysfunction: Relevance to Psychiatric Disorders

Tamar Gur[1], Therese Rajasekera[1], Aditi Vadodkar[1], Jacob Allen[2], and Michael Bailey[3]

[1]Ohio State University, College of Medicine, [2]Nationwide Children's Hospital, [3]Nationwide Children's Hospital, Ohio State University College of Dentistry

Background: Exposure to maternal stress in utero is linked to psychiatric disorders in the offspring. We examined the contribution of maternal stress and commensal microbes on the development of female anxiety and male social behavior in rodents.
Methods: Pregnant C57/BL6 females were assigned to stress or non-stressed control group. The stressed group were restrained for 2 hours/day between embryonic days 10-16. Placentas were collected from a cohort of pregnant females at E17.5. Microbial diversity was assessed by Illumina MiSeq platform, for targeted 16S ribosomal RNA gene sequencing. Offspring behavior was assessed in adulthood.
Results: Prenatal stress lead to alterations in the maternal, male, and female offspring intestinal microbial populations ($p<0.05$). There was a trend for placental microbes to be different in stressed vs. non-stressed animals ($p=0.08$). Sex differences emerged in the placental response to prenatal stress; female placentas and fetal brains demonstrated increased IL-1beta ($p<0.05$) and decreased BDNF ($p<0.05$), whereas in males, changes were primarily related to serotonin and cortisol. In adult female offspring alterations in cognition in the novel object recognition task ($p<0.05$) and anxiety-like behavior in the elevated plus maze ($p<0.05$) were associated with increased amygdala cytokine and decreased BDNF expression ($p<0.05$). In the male offspring, prenatal stress lead to decreased social interaction ($p<0.05$) and increased peripheral and brain serotonin, and an increased corticosterone response to social interaction ($p<.05$).
Conclusions: We have established a biomodel with behavioral alterations relevant to human psychiatric disorders allowing for through interrogation of the role of commensal microbes during gestation in the establishment of sex-differences in psychopathology.
Supported By: K08MH112892, KL2TR001068, and 2013 NARSAD Young Investigator Award to Tamar Gur
Keywords: Gut Microbiome, Prenatal Maternal Stress, Anxiety, Social Behavior

212. Maternal Gut Bacteria Promote Neurodevelopment Abnormalities in Mouse Offspring

Jun Huh[1]

[1]Harvard Medical School

Background: Accumulating evidence points to a central role for immune dysregulation during pregnancy as a risk factor in Autism Spectrum Disorder (ASD). Human epidemiological studies suggest that maternal viral infections early in pregnancy correlate with an increased frequency of ASD. This observation, coined maternal immune activation (MIA), has been modeled in rodents by inducing inflammation in pregnant dams. However, the immune cell populations critical in the MIA model have not been identified. We hypothesize Th17 cells and commensal bacteria inducing them in pregnant mice contribute to the development of MIA-associated phenotypes in offspring.
Methods: We examined the effect of MIA in pregnant dams selectively deficient for RORgt, a key transcription factor for Th17 cells, in T cells. We bred T cell−specific RORgt KO or WT females with C57BL/6 WT males. In another set of experiment, we pretreated pregnant dams with broad spectrum antibiotics to investigate if the presence of commensal bacteria play a critical role in this model.
Results: T cell-specific inactivation of RORgt in mothers or blocking activities of IL-17a protected against induction of MIA-dependent behavioral and neurodevelopmental phenotypes in offspring. In addition, we found that Th17 cell inducing bacteria in the maternal guts play critical roles in promoting MIA-associated phenotypes in offspring.
Conclusions: Using both genetic mutants and blocking antibodies targeting their activities, we demonstrated that Th17 cells and maternal gut bacteria are critical mediators of behavioral abnormalities as well as brain pathologies in MIA-affected offspring.
Supported By: Simons Foundation
Keywords: Autism Spectrum Disorder, Gut Microbiota, Immune System, Maternal Immune Activation, Cytokine

213. A Dysbiotic Intestinal Microbiota Harbored Within Patients With Anorexia Nervosa is Associated With Elevated Anxiety and Depression

Ian Caroll[1], Susan Kleiman[1], Eun Young Huh[2], Emily Bulik-Sullivan[1], Elle Glenny[1], Stephanie Thomas[1], Quyen Tang[1], Lisa Tarantino[1], and Cynthia Bulik[1]

[1]UNC Chapel Hill, [2]UTSA

Background: Anorexia nervosa (AN) affects 0.9% of women and 0.3% of men in the United States. Treatment outcome for AN is poor, it carries the highest mortality rate of any psychiatric disorder, and only half of patients experience long-term recovery. Despite significant morbidity and mortality, the evidence base for treatment is weak. Weight restoration approaches are typically guideline- rather than evidence-based and can be physically uncomfortable and psychologically

distressing to patients. Novel therapies for this illness are therefore needed, and the microbes in the intestine ("gut microbiota") have emerged as a potential target to improve treatment outcomes for AN.
Methods: We collected feces from patients with AN before and after clinical renourishment (n=16/10), and from sex- and age-matched healthy controls (n=91). The intestinal microbiota was characterized via high-throughput 16S rRNA gene sequencing. Additionally, we assessed levels of anxiety and depression in healthy controls and in patients with AN using the Beck Anxiety Inventory and Beck Depression Inventory-II.
Results: Patients with AN had significantly lower microbial diversity compared to healthy controls ($p<0.0001$), and this did not change after refeeding. Levels of anxiety and depression in patients with AN before refeeding were associated with the composition and diversity of the intestinal microbiota ($p=0.026$). No significant associations between gut microbial composition and diversity and levels of anxiety and depression were found in the healthy population surveyed.
Conclusions: These data provide evidence of an intestinal dysbiosis in AN, and an association between mood and the enteric microbiota in this patient population that is not observed in healthy controls.
Supported By: R01MH105684
Keywords: Intestinal Microbiota, Anorexia Nervosa, Depression and Anxiety

SYMPOSIUM
Genome-Wide and Systems Biology Approach in Epigenetic Studies of Hormonal Influence and Their Relevance to Posttraumatic Stress Disorder

12:30 p.m. - 2:30 p.m.
Chair: Gen Shinozaki
Co-Chair: Kerry Ressler

214. Genome-Wide DNA Methylation Analysis of High-Dose Synthetic Glucocorticoid Administration Across Peripheral Tissues and Brain in Humans

Patricia Braun[1], Benjamin Hing[1], Mai Tanaka-Sahker[1], Aubrey Chan[1], Lindsey Gaul[1], Yasunori Nagahama[1], Julian Robles[1], Jonathan Heinzman[1], Sayeh Sabbagh[1], Ellyn Cramer[1], Gabriela Duncan[1], Hannah Chicchelly[1], Sydney Jellison[1], Kumi Yuki[1], Liesl Close[1], Nicholas Coon[1], Mason Klisares[1], Theodosis Chronis[1], Brian Dlouhy[1], Matthew Howard[1], Hiroto Kawasaki[1], Kyle Stein[1], James Potash[2], and **Gen Shinozaki**[3]

[1]University of Iowa, [2]Johns Hopkins University, [3]University of Iowa Hospitals and Clinics

Background: An imbalance of glucocorticoids has been implicated in stress-related disorders. Within mouse models, differential methylation in response to glucocorticoid treatment has been shown. However, within humans the extent to which glucocorticoids affect DNA methylation (DNAm) across the genome is unknown.
Methods: In the initial analysis, buccal samples were collected from 30 subjects before and after dexamethasone treatment in the context of oral surgery. In an independent study of dexamethasone administration, samples were collected from 21 patients undergoing neurosurgical resection. This includes 21 subjects with saliva samples, 18 with blood, 13 with buccal, and 10 with brain. Genome-wide DNAm was assessed with the Infinium HumanMethylationEPIC array. Statistical significance was determined using the limma method, adjusting for age, sex, sample plate, and estimated surrogate variables.
Results: Within the initial analysis of buccal samples before and after dexamethasone, 6,453 CpGs were FDR significant at $p < 0.05$ and had differences greater than 10%. In the neurosurgical study, 1,397 CpGs in blood were nominally significant and overlapped with the initial analysis, 543 in buccal, 603 in saliva, and 275 in brain. Of the 275 CpGs in brain, 14 CpGs were also nominally significant in two of the three peripheral tissues in the neurosurgery cohort.
Conclusions: Synthetic glucocorticoid administration is significantly associated with DNAm changes within buccal samples. A subset of these CpGs were nominally significant in an independent study across peripheral tissues and in the brain. These findings provide initial evidence for an influence of glucocorticoids on DNAm across tissues within humans.
Supported By: K23MH107654
Keywords: Epigenetics, DNA Methylation, Corticosteroids, Glucocorticoids, PTSD - Posttraumatic Stress Disorder

215. DNA Methylation Across the Genome Associates With Serum Estrogen Levels and PTSD

Alicia Smith[1], Vasiliki Michopoulos[2], Stephanie Maddox[3], Laura Hack[2], Tanja Jovanovic[1], and Kerry J. Ressler[3]

[1]Emory University School of Medicine, [2]Emory University, [3]McLean Hospital, Harvard Medical School

Background: Women are at increased risk of developing posttraumatic stress disorder (PTSD) following trauma, and recent studies implicate estrogen as a contributing factor. This study leveraged samples from women with PTSD and animal models of fear learning to identify genes that contribute to PTSD in women.
Methods: We evaluated DNA methylation (HumanMethylation450) from blood of 278 female participants in the Grady Trauma Project and tested for association between each CpG site and outcome, controlling the false discovery rate (FDR) at 5%.
Results: PTSD associated with methylation of HDAC4, the gene that encodes histone deacetylase 4 (FDR<.05). The PTSD-associated CpG site in HDAC4 exhibited genotype-dependent methylation based on a nearby variant, rs7570903 ($p=0.0017$). This polymorphism associated with HDAC4 expression ($p=.049$), fear-potentiated startle ($p=.026$) and resting state functional connectivity of the amygdala ($p<.05$). Using auditory fear learning, we observed higher Hdac4 mRNA expression in the amygdala of ovariectomized female mice ($p=0.015$), and naturally-cycling metestrous females ($p=0.0001$). Finally, since serum estradiol associated with

>18,000 CpG sites across the genome (FDR<.05), developed a DNA methylation-based predictor of estradiol using random forests (RFs). After dividing the cohort into training (70%) and testing (30%) groups, we identified a set of 92 CpG sites that predicts estradiol levels in the testing set with strong correlation (r=0.82; p<2.6e-16).
Conclusions: Together, these results support an estrogenic influence contribution to PTSD and suggest that HDAC4 regulation may contribute to that risk. The estrogenic predictor developed for this study will serve as a resource for future epigenetic studies of psychiatric disorders in women.
Supported By: NARSAD; NIMH
Keywords: Estrogen, Women, Epigenetic, Translational Research, Trauma

216. Thyroid Hormones and Their Influence on Expression in Humans and an Animal Model of Trauma Exposure

Stephanie Maddox[1], Michelle Chen[1], Brianpaul Robert[1], Anya Levendusky[1], Guia Guffanti[2], Alicia Smith[3], and Kerry Ressler[2]

[1]McLean Hospital, [2]Harvard Medical School, McLean Hospital, [3]Emory University School of Medicine

Background: The thyroid hormone (TH) system has long been associated with anxiety and depression; however, it remains unclear how THs may contribute to trauma response and PTSD. A combination of nonbiased and targeted approaches in mice exposed to fear conditioning, a trauma model, and human clinical populations were used to examine this relationship.
Methods: Nonbiased RNA-sequencing and targeted qPCR were used to examine gene regulation in the amygdala of fear conditioned mice. Amygdala manipulation of THs was used to examine their role in anxiety and traumatic memory formation. Using data from the Grady Trauma Project (GTP), with Genome Wide Association Studies (GWAS) on over 6,000 subjects, we analyzed the predictive power of a polygenic risk score (PRS) for TH function on risk for PTSD and related symptomatology. Candidate gene analyses for TH-related genes revealed in our rodent RNAseq experiment were applied to GWAS data to examine their association with PTSD.
Results: Ten TH-related genes in the murine amygdala were regulated in response to conditioning (q< 0.05). THs were observed to be anxiogenic, enhance expression of traumatic memory, and gene expression (all p's<0.05) in mice. GTP-GWAS data revealed two missense SNPs within the Trip11 locus, a TH receptor coactivator, that associated with PTSD (p<0.008). The utility of the TH function PRS in PTSD risk and associated symptomatology is discussed.
Conclusions: Combined rodent models of trauma exposure and human clinical genetics reveal a novel association of THs and PTSD. Future studies will be needed to mechanistically examine the association of THs and PTSD.
Keywords: Thyroid Hormones, PTSD, Polygenic Risk Score, Amygdala, Fear Conditioning

217. Integrative Systems Approach Identifies HPA-Axis Related Gene Networks in PTSD

Nikolaos Daskalakis[1] and Kerry Ressler[1]

[1]Harvard Medical School/McLean Hospital

Background: Basal and challenge-induced hypothalamic–pituitary–adrenal axis alterations have been described in PTSD. However, the molecular basis of these hormonal findings involvement remains elusive.
Methods: Using Weighted correlation network analysis (WGCNA), we analyzed blood genome-wide expression data sets of peripheral blood from two large cross-sectional studies with and without PTSD, one civilian (n=565, 70% females) and one military (n=189, 14% females). For these cohorts, also genetically-predicted differential gene expression (gDGE) by PrediXcan method, differential gene methylation (DGM), and differential gene expression (DGE) signatures were available, together with pre- and post- dexamethasone plasma levels of cortisol.
Results: Using Weighted correlation network analysis (WGCNA) we detected 117 modules in the civilian cohort and 82 modules in the military cohort. Modules were then prioritized based on between-cohort conservation, correlation with the HPA-axis traits, and enrichment for gDGE, DGM and DGE. Among the most promising networks, there was a large (>100 genes) co-expression module showing large differences in connectivity between PTSD and non-PTSD and enrichment with genes related to the innate immune response.
Conclusions: HPA-axis related immune networks are associated with trauma-related individual differences in blood and brain, and can be the basis of treatment for PTSD.
Supported By: NIH, DOD and NARSAD
Keywords: Gene Networks, Gene Expression, Genetics, DNA Methylation, HPA Axis

SYMPOSIUM
Bayesian Multi-Level Approaches for Integrating Psychiatric Data Across Units of Analyses
12:30 p.m. - 2:30 p.m.
Chair: Martin Paulus

218. Multi-Block Models for Multivariate Neuropsychiatric Data

Wesley Thompson[1] and Martin Paulus[2]

[1]UCSD, [2]Laureate Institute for Brain Research

Background: The Research Domain Criteria (RDoC) initiative was launched by the NIMH in 2009, with the goal of finding new ways of classifying mental illnesses that are based on dimensions of observable behavioral and neurobiological measures. This initiative thus depends on integrating data across multiple longitudinal modalities ("blocks"), including genetics, epigenetics, brain imaging, self-report measures, among others.

Methods: We present a unified modeling framework for high-dimensional blocked multivariate longitudinal data, capable of handling irregularly sampled ("sparse") longitudinal data. Methods such as consensus PCA, and generalized canonical correlation analysis can be helpful in this context. In this talk we place such models into a Bayesian latent variable framework (reduced-rank covariance models).
Results: We apply these models to two examples of multimodal imaging datasets, one involving a longitudinal study of alcohol use (NCANDA), and the second the Tulsa 1000 (T1000) study. In the NCANDA study, we show that Cortical Thickness ROIs and NIH Toolbox measures demonstrate a differential relationship to substance use by age, so that younger adolescents are more vulnerable. For the second dataset, we uncover a latent factor associated with substance use that loads on (worse) performance for a block of neuropsychiatric measures and another block of cortical thickness measures.
Conclusions: Multi-block methods can be placed in a Bayesian latent variable framework deriving from the class of reduced-rank covariance models. We argue that this approach is beneficial for addressing the goals of RDoC and demonstrate its utility on data from two large multivariate neuropsychiatric studies.
Supported By: Laureate Institute for Brain Research
Keywords: Research Domain Criteria (RDoC), Biostatistics, Bayesian Model, Multivariate Analysis, Longitudinal Brain Imaging

219. General Factor Analysis Reveals Latent Variables Connecting Media Activity to Psychopathology in the ABCD Cohort

Martin Paulus[1], Wes Thompson[2], Susan Tapert[2], Florence Breslin[1], and Amanda Sheffield Morris[1]

[1]Laureate Institute for Brain Research, [2]University of San Diego, California

Background: Media activity is among the most important recreational behavior adolescents engage in, however, its impact on development, and the risk and resilience contributions to the development of high risk behaviors is not well understood. The Adolescent Brain Cognitive Development (ABCD) Study focuses on brain development throughout adolescence to understand the effects and integration of genetics, epidemiology and neurodevelopment in a large, inclusive sample. This investigation aimed to establish the latent variables that link internet activity to psychopathology in the ABCD cohort.
Methods: Briefly, 4524 male and female subjects age 9-10, which had been recruited between September 2016 and August 2017 were eligible for this analysis. Group factor analysis (GFA) was used to identify the latent variables (LV) that relate to media activity.
Results: GFA identified 6 robust LVs accounting for approximately 50% of the variance: (1) a relationship between low scores on socio-economic variables, high scores on media activity and psychopathology, and scores on cognitive task performance; (2) gender-specific performance on cognitive task, high media activity, and high psychopathology. At high risk for future substance use (n= 1876) individuals showed greater loading on the LV 1 ($t = -7.0994$, $df = 3949.7$, p-value $= 1.479e-12$)
Conclusions: (1) media activity is complex and cannot be described by a single variable, (2) a specific combination of socio-demographics, cognitive function, and media activity is related to increased psychopathology, and (3) substance use risk status can be related to a specific aspect of media activity.
Supported By: U01DA041089
Keywords: Internet, Cognition, Adolescents, Psychopathology, Substance Use

220. Childhood Adversity Disrupts Cognitive Control Development and Function

Amy Peters[1], Meghan Quinn[2], Katie Bessette[1], Lisanne Jenkins[3], Jonathan Stange[1], David Marshall[4], Melvin McInnis[4], Kelly Ryan[4], and **Scott Langenecker**[1]

[1]University of Illinois at Chicago, [2]Vanderbilt University, [3]Northwestern University, [4]University of Michigan

Background: Childhood adversity results in increased risk for a number of psychiatric disorders. RDoC approaches provide the opportunity to understand the multi-level effects of childhood adversity (CA) upon cognitive control (CC) behavior and the supporting neural systems.
Methods: Sample 1 included 397 adults (ages 18-65) with and without bipolar illness. Sample 2 was 70 adolescents (ages 14-18) with and without depression. Sample 3 was 98 young adults (ages 18-23) with and without a history of depression. Sample 3 included seed based connectivity with prefrontal and inferior parietal seeds and gray matter volume (GMV) estimated using voxel based morphometry. Current depression symptoms were covaried in all regression models. CC was measured with a Parametric Go/No-go Test. CA was measured with the Childhood Trauma Questionnaire
Results: In sample 1, CA was a significant predictor of CC ($B = -.21$, $p < .0001$). In sample 2, CA was inversely correlated with CC at the trend level ($B = -.25$, $p = .058$). In sample 3, CA was predictive of CC ($B = -.27$, $p = .01$). CA was positively associated with connectivity (all ps $< .005$) from CC seeds to bilateral middle frontal and inferior parietal regions and inversely with connectivity to left orbital frontal gyrus. CA was negatively associated with right middle frontal GMV ($p < .0001$).
Conclusions: CA is related to disruptions in CC performance, elevated intra-CC network connectivity, and reduced GMV in right middle frontal gyrus. These effects are evident across diagnoses and a broad age spectrum, suggesting a developmental onset and stable effect.
Supported By: ROI MH091811, F31 MH108258, Heinz C. Prechter Research Fund
Keywords: Gray Matter Volume, Brain Connectivity, Cognitive Control, Mood Disorders, Childhood Trauma

221. Integrating Brain-Behavior Data to Identify Clinically Meaningful Biotypes for Depression and Anxiety

Leanne Williams[1]

[1]Stanford University

Background: Depression and anxiety involve catch-all diagnoses that lump together patients experiencing a wide range of symptoms with different underlying brain dysfunctions. We do not currently have a means to guide treatments that correct these underlying malfunctions.

One approach to addressing this need is the development of a taxonomy of circuit-based "biotypes", that connect distinct malfunctions of neural circuits to distinct behavioral profiles.

Methods: In a series of studies, we recruited 274 unmedicated patients spanning a range of mood and anxiety disorders, and a further 160 patients with additional comorbidities, such as substance use disorder. Patients were assessed with standardized common data elements, including functional brain imaging under rest and task-evoked conditions, behavioral testing and comprehensive symptom scales. To operationalize our taxonomy, we used a model-driven, construct validation approach, grounded in a published theoretical taxonomy (Williams, 2016; 2017). For each circuit-defined biotype, we tested relations with behavioral and symptom profiles, using both dimensional and extreme-group approaches.

Results: In general, linear models (with corrected alpha thresholds), biotypes based on malfunctions of intrinsic default, salience and attention circuits were related to specific profiles of rumination, anxious avoidance and cognitive symptoms. Biotypes based on task-evoked malfunctions in negative affect, threat, reward and cognitive control circuits were related to mood, fear, anhedonia and dis-inhibition symptoms. These types are reined with bayesian models.

Conclusions: Biotypes anchored in brain circuit malfunctions may account for specific symptom profiles that cut across traditional diagnostic categories. This approach lays a foundation for further data-driven approaches, and probing of circuit biotypes using targeted interventions.

Supported By: NIMH, NIH

Keywords: Biomarkers, Data-Driven Analytics, Major Depressive Disorder (MDD), Anxiety Disorder, Brain Imaging

SYMPOSIUM
Theta-Burst Vs. High-Frequency rTMS Effectiveness Evaluation in Depression (THREE-D): A Randomized Non-Inferiority Trial

12:30 p.m. - 2:30 p.m.

Chair: Jonathan Downar

222. Clinical Results From the Theta Burst Versus High Frequency Repetitive Transcranial Magnetic Stimulation Effectiveness Evaluation in Depression (THREE-D) Randomized Non-Inferiority Trial

Daniel Blumberger[1], Fidel Vila-Rodriguez[2], Kevin Thorpe[3], Kfir Feffer[4], Yoshihiro Nodaa[5], Peter Giacobbe[3], Yuliya Knyahnytska[1], Sidney H. Kennedy[4], Raymond W. Lam[2], Zafiris J. Daskalakis[1], and Jonathan Downar[6]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]University of British Columbia, [3]University of Toronto, [4]University Health Network, [5]Keio University, [6]University of Toronto, Center for Addiction and Mental Health, Toronto Western Hospital

Background: Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) using high frequency (10Hz) left-side dorsolateral prefrontal cortex (DLPFC) stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37.5 min for a standard 10Hz treatment session.

Methods: This multi-site, randomized, non-inferiority clinical trial compared the effectiveness, safety and tolerability of iTBS versus 10Hz-rTMS. We randomized 414 participants aged 18-65 with a current treatment-resistant major depressive episode to a course of 4-6 weeks of 10Hz or iTBS to the left DLPFC. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17); secondary outcomes included response and remission rates, safety and tolerability. Non-inferiority margins were defined at 2.25 difference on HRSD-17, and at 15% and 10% for response/remission rates respectively.

Results: HRSD-17 scores improved from 23.5±4.3 to 13.1±7.6 for 10Hz and 23.4±4.2 to 13.1±7.9 for iTBS (adjusted difference, -0.052, 95%CI -1.35, $p=0.0028$), establishing non-inferiority for iTBS. Response/remission rates were 48.6%/28.2% for 10Hz and 50.5%/33.1% for iTBS (adjusted differences, 2.0/5.1%, 95%CIs -7.0%/-3.1%, $p<0.001$), consistent with non-inferiority for iTBS. Self-rated pain was slightly higher for iTBS versus 10Hz (3.8/10±2.0 versus 3.4/10±2.0, $p=0.028$); however, dropout rates did not differ between groups (10Hz, 6%; iTBS, 8%; $p=0.655$).

Conclusions: In patients with medication-resistant depression, iTBS achieved non-inferior status for reduction in depression symptoms versus 10Hz rTMS as well as for response/remission rates. Both treatments had low drop-out rates and similar tolerability.

Supported By: Canadian Institutes of Health Research MOP-136801, Temerty Family Foundation and Campbell Family Mental Health Research Institute at the Centre for Addiction and Mental Health, the Edgestone Foundation and Tina Buchan at the University Health Network.

Keywords: Depression, rTMS, Theta Burst, Treatment Resistant Depression

223. Anterior Cingulate Cortex Connectivity and Treatment Response Prediction to rTMS in Depression

Fidel Vila-Rodriguez[1], Jonathan Downar[2], Daniel M. Blumberger[3], and Ruiyang Ge[1]

[1]University of British Columbia, [2]University of Toronto, Center for Addiction and Mental Health, Toronto Western Hospital, [3]Centre for Addiction and Mental Health, University of Toronto

Background: Connectivity measures involving several loci within the anterior cingulate cortex have been shown to predict response in MDD. However, no direct comparison of predictive power of these regions has been attempted. We aimed at investigating the predictive accuracy of the subgenual anterior

cingulate cortex (sgACC) and the rostral cingulate cortex (rACC)
Methods: 62 patients with treatment resistant depression were recruited and randomized to receive either 10Hz rTMS or intermittent Theta Burst Stimulation to the Left-Dorsolateral Prefrontal Cortex (DLPFC). Resting State fMRI was acquired before treatment initiation and a priori seed-driven functional connectivity analysis was conducted to discover connectivity pairs to investigate their outcome predictive capacity.
Results: Functional connectivity between sgACC-DLPFC and rACC-right lateral parietal cortex (LPC) demonstrated classification accuracy rate of 84% (AUC 0.87; CI, 0.76 to 0.98; $p<0.001$) and 76% (AUC 0.75; CI, 0.61 to 0.89; $p=0.001$) respectively. Furthermore, higher connectivity values in sgACC-DLPFC were associated with more improvement of symptoms, while higher connectivity values in rACC-LPC were associated to less improvement of symptoms.
Conclusions: Functional connectivity patterns of sgACC and rACC may provide predictive biomarkers of treatment response to rTMS
Supported By: Brain Canada
Keywords: rTMS, Depression, Prediction of Treatment Outcome, fMRI Resting State, EEG

224. Resting-State fMRI Predictors and Mechanisms of rTMS Treatment Response: Neuroimaging Results of the Three-D Study

Katharine Dunlop[1], Sarah K. Peters[1], Peter Giacobbe[2], Zafiris Daskalakis[3], Raymond W. Lam[4], Sidney Kennedy[5], Fidel Vila-Rodriguez[4], Daniel M. Blumberger[6], and Jonathan Downar[7]

[1]University of Toronto, [2]University of Toronto, Center for Addiction and Mental Health, University Health Network, [3]Centre for Addiction and Mental Health, [4]University of British Columbia, [5]University Health Network, [6]Centre for Addiction and Mental Health, University of Toronto, [7]University of Toronto, Center for Addiction and Mental Health, Toronto Western Hospital

Background: Conventional rTMS for treatment-resistant depression (TRD) targets the dorsolateral prefrontal cortex (DLPFC) using 10 Hz stimulation over 37.5 minutes. Briefer protocols like intermittent theta burst (iTBS) has the potential to improve treatment accessibility. However, it is not fully understood what aspects of brain connectivity are associated with either/both rTMS protocols. The aim of this study was to identify resting-state fMRI predictors and mechanisms of antidepressant response to 10 Hz and iTBS stimulation over the left DLPFC.
Methods: 303 MDD patients randomized to either once daily iTBS or 10 Hz over left DLPFC for 4-6 weeks were included. Primary treatment outcomes included the 17-item Hamilton Rating Scale for Depression and Beck Depression Inventory. On MRI, patients underwent a T1 anatomical and 10-minute resting-state functional scan before and after treatment. We completed a seed-to-voxel based approach using cortical and striatal seeds to identify predictors and mechanisms of treatment response.
Results: Among all participants, low baseline connectivity stemming from nodes of the salience network corticostriatal loop were predictive of response for both iTBS and 10Hz rTMS (cluster $p<0.01$). Furthermore, increases in salience network corticostriatal connectivity from pre- to post-rTMS accompanied antidepressant response (cluster $p<0.01$).
Conclusions: Imaging results identified predictors and correlates of antidepressant response that implicates network-level corticostriatal loops. This study represents a step to understanding maladaptive network interactions in MDD, and the impact of non-invasive brain stimulation techniques on modulating brain network connectivity.
Supported By: CIHR; Edgestone Foundation
Keywords: Major Depressive Disorder (MDD), Repetitive Transcranial Magnetic Stimulation, Resting state fMRI, Dorsolateral Prefrontal Cortex

225. Follow-On Studies From the THREE-D Trial: Preliminary Clinical and Neuroimaging Findings

Jonathan Downar[1], Peter Fettes[1], Katharine Dunlop[1], Sarah K. Peters[1], Fidel Vila-Rodriguez[2], Raymond W. Lam[2], Sidney Kennedy[3], Zafiris Daskalakis[4], and Daniel Blumberger[4]

[1]University of Toronto, [2]University of British Columbia, [3]University Health Network, [4]Centre for Addiction and Mental Health

Background: The THREE-D trial generated a set of findings with important translational implications. These include the non-inferiority of 3 min iTBS over 37.5 min conventional 10 Hz sessions, and the identification of structural and functional neuroimaging predictors and correlates of response to left DLPFC-rTMS with each protocol. These advances may enable several novel approaches to further improve the clinical utility of rTMS: multi-session treatment, multi-target treatment, and personalized target selection. Preliminary demonstrations of each of these approaches are now available.
Methods: We present preliminary findings for follow-up studies from THREE-D, including randomized comparisons of clinical outcomes for once- versus twice-daily iTBS to left DLPFC in unipolar depression ($N=200$), and for brief protocols targeting alternative sites in dorsomedial prefrontal cortex (DMPFC) and right orbitofrontal cortex (rOFC) in unipolar depression ($N=150$), with accompanying analyses of resting-state fMRI predictors and correlates of outcome from pre- and post-treatment scans.
Results: In these preliminary analyses, compared to once-daily rTMS, twice-daily rTMS significantly accelerated the pace of improvement over the first 15 sessions ($p<0.05$) but did not lead to superior outcomes at 30 sessions($p=$n.s.); acceleration was markedly heterogeneous across individuals. Resting-state fMRI revealed distinctive predictors and correlates of response to DMPFC- vs. rOFC-rTMS, in terms of dorsal anterior cingulate vs. ventral striatal connectivity, at a conservative family-wise error threshold ($p<0.01$).
Conclusions: Brief stimulation protocols enable accelerated rTMS regimens of multiple daily sessions. Stimulating the DLPFC more than once daily may accelerate improvement

among responders, without increasing remission rates. Stimulating additional sites (DMPFC,rOFC) engages different neural circuits, and could thereby lead to higher overall remission rates.

Supported By: Brain Canada, CIHR, Toronto General and Western Hospital Foundation

Keywords: rTMS, MDD, Resting State fMRI, Clinical-Trial

SYMPOSIUM
Longitudinal Biomarkers for Stress Resilience: A Translational Perspective

3:00 p.m. - 5:00 p.m.

Chair: Christiaan Vinkers

Co-Chair: Nikolaos Daskalakis

226. Elucidating Populations, Mechanisms and Markers Through the Utilization of Stress Challenges

Isaac Galatzer-Levy[1]

[1]Mindstrong Health

Background: Dr. Galatzer-Levy will present results from cohort study of individuals (n=157) exposed to a life-threatening event and subsequently admitted to the emergency room at Bellevue Hospital in New York City. Dr. Galatzer-Levy will present on novel methods for identifying stress reactive markers as they predict the course of posttraumatic stress pathology following exposure.

Methods: Changes in heat signature in the extremities and core were measured via infrared camera along with concordant measurements of skin conductance and clinical assessments of stress pathology.

Results: Results indicated that changes in temperature, measured with infrared, in the extremities and core were positively correlated PTSD severity r (extremities) = .30, $p < .05$, r (core)= .36, $p \leq .05$. These measures were also associated with concurrent changes in autonomic arousal measured via skin conductance (r= .31, p<=;.0001).

Conclusions: Together, results indicate that changes in temperature distribution in response to free recall of traumatic events is a marker of autonomic arousal and is associated with stress pathology. This work demonstrates that novel physiological assessments that can be measured non-invasively can provide information about risk for stress related psychopathology.

Supported By: NIMH K01MH102415

Keywords: PTSD, Autonomic Reactivity, Methods, Skin Conductance

227. Longitudinal Changes in Glucocorticoid Receptor Exon 1F Methylation as a Biomarker for Psychopathology After Military Deployment

Remmelt Schur[1], Marco Boks[1], Bart Rutten[2], Nikolaos Daskalakis[3], René Kahn[4], Marian Joels[5], Elbert Geuze[6], Eric Vermetten[7], and **Christiaan Vinkers**[4]

[1]University Medical Center Utrecht, [2]Maastricht University Medical Centre, [3]Harvard Medical School/McLean Hospital, [4]Brain Center Rudolf Magnus, University Medical Center Utrecht, [5]University Medical Center of Groningen, [6]Military Mental Healthcare, [7]Leiden University Medical Center

Background: Several cross-sectional studies have demonstrated the relevance of DNA methylation of the glucocorticoid receptor exon 1F region (GR-1F) for trauma-related psychopathology. We conducted a longitudinal study to examine GR-1F methylation changes over time in relation to trauma exposure and the development of post-deployment psychopathology.

Methods: GR-1F methylation (52 loci) was quantified using pyrosequencing in whole blood of 92 military men one month before and six months after a four-month deployment period to Afghanistan. GR-1F-wide methylation (mean methylation and the number of methylated loci) and functional methylation (methylation at loci associated with GR exon 1F expression) measures were examined. We investigated the effect of exposure to potentially traumatic events during deployment on these measures. Subsequently, changes in GR-1F methylation were related to changes in mental health problems (Symptom Checklist 90) and PTSD symptoms (Self-Report Inventory for PTSD).

Results: Trauma exposure during deployment was significantly associated with an increase in methylation (mean methylation: $\beta=0.040$, $P=0.003$; number of methylated loci: $\beta=0.75$, $P=0.002$; functional methylation: $\beta=0.56$, $P=0.002$) and increased methylation at 23 individual CpGs. The development of mental health problems was significantly associated with an increase in functional methylation ($\beta=0.010$, $P=0.005$). The development of PTSD symptoms was not associated with change in any methylation measure (all P-values >0.12). Predeployment methylation did not predict post-deployment mental health problems (mean methylation: AUC=0.51-0.54, $P>0.47$) or PTSD symptoms (AUC=0.56-0.58, $P>0.10$).

Conclusions: This is the first study to prospectively demonstrate trauma-related increases in GR-1F methylation and it suggests that only increases at specific functionally relevant sites predispose for post-deployment psychopathology.

Supported By: This study was funded by a grant from the Dutch Ministry of Defence.

Keywords: MDD, PTSD, Trauma Exposure, Epigenetic Biomarkers, Glucocorticoid Receptor

228. Transcriptome-Wide Analysis Identifies ICAM5 Differentially Expressed in Chronic PTSD Symptoms Versus Resiliency Post Trauma Exposure in a Longitudinal Study

Aliza Wingo[1], Nikolaos Daskalakis[2], Isaac Galatzer-Levy[3], Ryan Richholt[4], Vasiliki Michopoulos[5], Adriana Lori[5], Guia Guffanti[6], Barbara Rothbaum[7], Tanja Jovanovic[7], Amanda Myers[8], Matt Huentelman[4], Charles Nemeroff[9], and Kerry Ressler[2]

[1]Atlanta VAMC/Emory University School of Medicine, [2]Harvard Medical School/McLean Hospital, [3]Mindstrong Health, [4]T-gen, [5]Emory University, [6]Harvard T.H. Chan School of Public Health, [7]Emory University School of Medicine, [8]Miami University, [9]University of Miami Health System

Background: Following a trauma, some develop PTSD while others stay resilient to its sequelae. We have limited knowledge on the biological underpinnings of resilience to stress.
Methods: Participants were recruited from emergency departments following a trauma. Blood was drawn in the aftermath of trauma exposure for transcriptomic characterization. Follow-up assessments were completed at 1, 3, 6, and 12 months post-trauma to assess PTSD symptom development using the modified PTSD Symptom Scale (PSS). PTSD symptom severity trajectories based on PSS total scores across 1, 3, 6, and 12 months were identified using the Latent Growth Mixture Modeling. Transcriptome-wide differential analysis was performed using Voom/Limma.
Results: The three main symptom trajectories were: Recovery (2.0%), Resilient (80.9%), and Chronic PTSD symptoms (17.1%). In a subset of participants with RNA-seq data, 169 were Resilient and 33 had Chronic PTSD symptoms. Transcriptome-wide differential analysis for Resilient versus Chronic identified Intercellular Adhesion Molecular 5 (ICAM5) in the top two most differentially expressed genes after adjusting for sex, age, site, and batch (N=202, p=7.02 x 10-5, adjusted p=0.49). ICAM5 is expressed on neurons and critical for neuron-microglia interactions. Additionally, ICAM5 involvea in immune privilege of the brain and acts as an anti-inflammatory agent. Analysis of a larger set is in progress.
Conclusions: We combined transcriptomes with trajectories of PTSD symptom development using longitudinal data. While ICAM5 association needs replication, ICAM5 involves important functions in both brain and immune systems. Hence, ICAM5 holds promise as a window into further understanding of biological underpinning of resilience vs. susceptibility to trauma exposure.
Supported By: R01-MH094757; IK2CX000601
Keywords: PTSD - Posttraumatic Stress Disorder, Longitudinal Study, Transcriptomics, Resilience

229. Psychophysiological Biomarkers Predicting the Development of PTSD: An Emergency Department Prospective Longitudinal Study

Tanja Jovanovic[1], Rebecca Hinrichs[1], Sanne van Rooij[1], Vasiliki Michopouolos[1], Sterling Winters[1], Barbara Rothbaum[1], and Kerry Ressler[2]

[1]Emory University, [2]Harvard University, McLean Hospital

Background: Post-traumatic stress disorder (PTSD) is a complex and heterogeneous disorder that can develop in 10-20% individuals who are exposed to a traumatic event. Neuroimaging studies show that brain activity can predict who will be at risk for PTSD after trauma exposure (Stevens et al., 2017; van Rooij et al., 2017). However, MRI is not always a feasible prediction method, and more easily accessible, low-cost methods are needed. Skin conductance response (SCR) to trauma reminders has been shown to be associated with PTSD (Orr/Pitman), and can be captured by mobile devices (Hinrichs et al., 2017). The present study used a mobile measure of SCR to trauma in the Emergency Department (ED) as a predictor of PTSD symptoms six months later.
Methods: Participants (n=54) were recruited from an ED within 6 hours of exposure to trauma. SCR was assessed using the eSense system (Mindfield Biosystems, Inc.) on an iPad during the Standard Trauma Interview. PTSD symptoms were assessed at 6 months after trauma using the PTSD Symptom Scale (PSS).
Results: SCR to the trauma reminder was significantly correlated with PSS at 6 months post-trauma, controlling for demographics and baseline PTSD and Depression ($r=0.82$, $p<.0001$). Logistic regression showed that SCR immediately post-trauma significantly predicted PTSD diagnosis at 6-months following the trauma ($F=44.58$, $p<0.0001$).
Conclusions: The current results show that SCR to trauma-relevant stimuli collected in the immediate aftermath of trauma is predictive of PTSD development 6-months later. While autonomic biomarkers have shown predictive value, the advances in technology allow for mobile use of this method.
Supported By: NIH R01, U01
Keywords: PTSD - Posttraumatic Stress Disorder, Psychophysiology, Biomarkers, Skin Conductance, Trauma Exposure

SYMPOSIUM
Biological Indices of Stress-Related Accelerated Aging and Associated Health Outcomes
3:00 p.m. - 5:00 p.m.
Chair: Erika Wolf

230. Traumatic Life Experiences are Associated With Increases in Epigenetic Aging

Morgan Levine[1]

[1]Yale Medical School

Background: Experiences of trauma have been linked to increased risk for a number of chronic health conditions. One potential pathway through which social trauma may influence health is via alterations in the rate of biological aging. We recently developed a highly accurate candidate biomarker of aging based on DNA methylation (DNAm) levels in blood, which is predictive of a number of age-related morbidity/mortality outcomes.
Methods: Using data on 2,029 females from the Women's Health Initiative, we examined whether women who recently experienced a higher number of traumatic life events showed increases their "epigenetic aging". Epigenetic age was measured using our new biomarker, based on DNA methylation levels at 513 CpG sites. Death of a spouse, death of a friend, divorce, major money problems, major conflict with child, major accident or disaster, physical abuse, and verbal abuse were the events considered and were used to create a continuous variable of number of events experienced, and an ordinal variable (0 vs. 1, 2, or 3+). OLS models, adjusted for race/ethnicity, education, chronological age, and smoking status were used to examine the association between trauma and epigenetic age.
Results: Those who experienced more traumatic events over the past year had significantly older epigenetic ages, relative to their chronological ages. Results remained consistent when

examining the number of events as a continuous variable (p=0.003) or when looking at dose-response.
Conclusions: Overall, our results suggest that one process in which experiences of trauma may impact health is via its effect on the biological aging process.
Keywords: Aging, DNA Methylation, Psychosocial Stress, Trauma Exposure

231. Posttraumatic Psychopathology and a Quickening Pace of the Epigenetic Clock

Erika Wolf[1], Mark Logue[2], Filomene Morrison[3], Anjanette Stone[4], Steven Schichman[4], Regina McGlinchey[5], William Milberg[5], and Mark Miller[6]

[1]National Center for PTSD at VA Boston Healthcare System, [2]National Center for PTSD, [3]Boston University & VA Boston Healthcare System, [4]Pharmacogenomics Analysis Laboratory, Research Service, Central Arkansas Veterans Healthcare System, [5]Harvard Medical School & VA Boston Healthcare System, [6]Boston University & VA Boston Healthcare System, National Center for PTSD

Background: Advances in the study of biological aging have identified that DNA methylation data can be used to index cellular age and to evaluate pathogenic factors that accelerate aging. Stress, trauma, and posttraumatic stress disorder (PTSD) have been cross-sectionally associated with advanced DNA methylation age relative to chronological age, however longitudinal investigation is lacking. The aim of this study was to examine longitudinal associations between an array of posttraumatic psychiatric conditions and the pace of the epigenetic clock.
Methods: 179 veterans (88% male, mean age = 33 years) completed two assessments spanning approximately two years. Whole blood DNA methylation was interrogated via the Illumina EPIC beadchip and two indices of DNA methylation age quantified. Psychiatric diagnoses were assessed via structured interview. The pace of the epigenetic clock was operationalized as the difference between age estimates over time as a function of time between assessments.
Results: In regressions, PTSD symptoms defined by avoidance of trauma-related cues and emotional numbing (p = .02) and alcohol-use disorders (p = .001) at time 1 were associated with an increasing pace of the epigenetic clock. Alcohol-use disorders were associated with 1.58 years in epigenetic age acceleration for every year between assessments.
Conclusions: This is the first study to suggest that posttraumatic psychopathology is associated with a quickening pace of the epigenetic clock over time. This carries implications for understanding premature onset of age-related diseases among individuals with chronic psychopathology. It suggests that accelerated cellular aging may be a shared consequence across stress-related psychiatric symptoms.
Supported By: US Dept of VA, CSR&D Merit Review Award Number I01 CX-001276-01; NIMH R21MH102834; NIMH 5T32MH019836-16
Keywords: Chronic Stress, Cellular Aging, Epigenetics, Longitudinal Cohort, Alcohol Use Disorder

232. Mechanisms of Accelerated Cognitive Aging in PTSD

Bret Rutherford[1], Yuval Neria[2], Scott Small[3], Adam Brickman[3], Adam Ciarleglio[3], and Frank Provenzano[3]

[1]Columbia University & New York State Psychiatric Institute, [2]Columbia University Medical Center, New York State Psychiatric Institute, [3]Columbia University

Background: Older PTSD patients exhibit faster cognitive decline and have twice the risk of dementia compared to individuals without PTSD. Accelerated biological aging may explain these findings, as PTSD is associated with similar brain changes to those occurring with cognitive aging, including bilateral hippocampal volume reductions and increased microvascular lesions. This presentation describes ongoing work from our laboratories evaluating dentate gyrus (DG) metabolism and DG-dependent cognition as mechanisms of accelerated cognitive decline in PTSD.
Methods: In preliminary studies, adults with PTSD (N=15) were assessed with the Clinician Administered PTSD Scale (CAPS) and cerebral blood flow (CBV)-fMRI. In addition, individuals with PTSD (N=16) and age-matched healthy controls (N=9) were evaluated using a modified form of the Benton Visual Retention Task (ModBent), which we have previously demonstrated to be DG-dependent. Data collection for a larger version of these studies is ongoing.
Results: In a linear regression of CAPS score on CBV values in 6 regions of interest (right and left posterior DG, mid DG, and anterior DG), a significant ($p<0.05$) negative correlation was found between right anterior DG CBV and CAPS score. ModBent performance declined with increasing age with moderate effect size magnitude (r=0.30) in PTSD patients but not controls (r=-0.18).
Conclusions: PTSD is associated with relative hypometabolism in the right anterior DG and potentiated age-related decline in DG-dependent cognitive function. These findings are consistent with the hypothesis that PTSD and brain aging constitute a "double hit" to DG/CA3 that contributes to the negative health and functional outcomes suffered by older PTSD patients.
Supported By: NIMH R01 MH111596
Keywords: PTSD - Posttraumatic Stress Disorder, Brain Aging, Hippocampus, Cerebral Blood Flow

233. Indices of Cellular Health are Associated With Antidepressant Treatment Response

Daniel Lindqvist[1], Christina Hough[2], Victor Reus[2], Alexandra Morford[2], Jue Lin[2], Jill James[3], Francesco Saverio Bersani[4], Elissa Epel[2], Synthia H. Mellon[2], and Owen Wolkowitz[2]

[1]Lund University/UCSF, [2]University of California, San Francisco, [3]University of Arkansas, [4]Sapienza University of Rome

Background: Accelerated cellular aging, evidenced by shortened leukocyte telomere length (LTL), has been reported in Major Depressive Disorder (MDD), and may convey an increased risk for somatic co-morbidity. Shortened LTL reflects a cell's mitotic history, cellular "age" and cumulative exposure to inflammation and oxidation, as well as the availability of telomerase, a telomere-lengthening enzyme. Telomere shortening leads to replicative senescence and cellular malfunctions including oxidative stress, mitochondrial damage, and apoptosis. Here we present data linking indices of accelerated cellular aging to worse antidepressant treatment response in MDD.
Methods: Unmedicated MDD subjects were assessed before and after 8-weeks of open-label SSRI treatment.
Results: Lower antidepressant treatment efficacy was associated with i) shorter pre-treatment LTL ($p<0.05$, $n=27$), ii) smaller increases in telomerase activity over the course of treatment ($p<0.01$, $n=16$), iii) higher levels of oxidative stress markers pre-treatment ($p<0.01$, $n=22$), and iv) a greater increase in oxidative stress during treatment ($p<0.05$, $n=22$). Circulating cell free mitochondrial DNA (CCf-mtDNA), a potential marker for mitochondrial stress and cellular damage, was highly elevated was highly significantly elevated in unmedicated MDD compared to healthy controls ($p<0.00001$, $n=105$), and ccf-mtDNA increased during treatment in non-responders, but not in responders ($p=0.02$, $n=19$).
Conclusions: Our data show, from multiple indices of cellular health, that accelerated cellular aging or damage is associated with poorer antidepressant response in MDD. Cellular health may be an important moderator of successful antidepressant response.
Supported By: NIMH; grant No. R01-MH083784, the O'Shaughnessy Foundation, the Tinberg family, the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC), and the Bernard and Barbro Foundation. This project was also supported by the National Institutes of Health/National

Center for Research Resources (NIH/NCRR) and the National Center for Advancing Translational Sciences, NIH (through UCSF-CTSI grant No. UL1 RR024131).

Daniel Lindqvist was supported by the Swedish Research Council (registration No. 2015-00387), Marie Skłodowska-Curie Actions, COFUND, Project INCA 600398, the Swedish Society of Medicine, the Söderström-Königska Foun-dation, the Sjöbring Foundation, OM Persson Foundation and the province of Scania (Sweden) state grants (ALF).
Keywords: Antidepressant Response, Oxidative Stress, Cellular Aging, mtDNA Copy Number, MDD

SYMPOSIUM
Transdiagnostic Neuromarkers of Emotion: From Bench to Bedside, Across Species & Development

3:00 p.m. - 5:00 p.m.
Chair: Alexander Shackman
Co-Chair: Amit Etkin

234. Neurogenetic Bases of Extreme Early-Life Anxiety

Alexander Shackman[1]

[1]University of Maryland College Park

Background: Children with an anxious temperament (AT) are at risk for anxiety disorders, depression, and substance abuse, underscoring the need to develop a deeper understanding of the underlying neurobiology.
Methods: Here, I will describe published and unpublished work leveraging multimodal brain imaging techniques (FDG-PET/fMRI/sMRI) in humans and monkeys. Monkeys are ideal for developing an understanding of the origins of extreme early-life anxiety; homologous genes and brains endow monkeys and children with a similar repertoire of defensive responses to novelty and potential threat, enabling similar procedures for quantifying trait-like differences in AT.
Results: Work using these methods ($p's<.05$) has revealed compelling evidence that AT—a heritable, multidimensional phenotype—reflects a distributed circuit encompassing the central nucleus of the amygdala (Ce), bed nucleus of the stria terminalis (BST), orbitofrontal cortex (OFC), and periaqueductal gray (PAG) ($n=592$). These regions show robust intrinsic functional connectivity in humans ($n=27$-130) and monkeys ($n=89$-378). Genetic correlation analyses indicate that this circuit can be fractionated into regions mediating heritable risk for the development of extreme anxiety (BST, OFC, PAG) vs. regions mediating risk associated with adverse experience (Ce). Reduced connectivity between Ce and prefrontal cortex is associated with heightened anxiety in monkeys ($n=89$) and pediatric anxiety patients ($n=28$). Elevated BST metabolism supports persistent anxiety following threat encounters ($n=23$-109) in monkeys and increased BST volume prospectively predicts elevated negative affect in daily life in humans ($n=44$; smart-phone experience-sampling).
Conclusions: These findings provide a framework for developing improved biomarkers of transdiagnostic risk and inform mechanistic work aimed at developing more effective interventions for pathological anxiety.
Supported By: This work was supported by the National Institutes of Health (DA040717, HD003352, HD008352, MH018931, MH046729, MH069315, MH081884, MH084051, MH091550, MH107444, OD011106, and RR000167), the HealthEmotions Research Institute, Meriter Hospital, and the University of Maryland, College Park.
Keywords: Fear, Anxiety, Individual Differences, Brain Imaging, Extended Amygdala (CeA/BST)

235. Novel Mechanisms of Fear Reduction Targeting the Biological State of the Developing Brain

Dylan Gee[1], Paola Odriozola[1], Luise Pruessner[2], Jason Haberman[1], and Emily Cohodes[1]

[1]Yale University, [2]Heidelberg University

Background: Anxiety disorders, which often emerge during adolescence, are characterized by difficulty discriminating between threatening and safe contexts. Translational studies

in developing mice and humans have demonstrated dynamic changes in frontoamygdala circuitry that supports extinction learning, raising the question of whether adolescents with anxiety disorders may benefit from efforts to optimize fear reduction through novel mechanisms that rely on alternate neural circuitry.
Methods: The present (unpublished) study tested the efficacy of safety cues to reduce amygdala reactivity during development (6-30 years old; N=45) using a conditioned inhibition task that was modified for use in an MRI scanner with a developmental sample.
Results: Findings revealed behavioral and psychophysiological (skin conductance) evidence of safety learning, and the safety cue effectively reduced SCR to a greater extent than extinction in children and adolescents, but not in adults ($p<.001$). We demonstrated for the first time, to our knowledge, that children and adolescents both showed robust hippocampal activation to the CS+ paired with the safety cue ($p<.05$, corrected), recapitulating the same neural target that has previously been shown in non-human animals and filling a significant translational gap. Interestingly, only adolescents showed increased medial prefrontal cortex activation ($p<.05$, corrected) and downregulation of amygdala reactivity associated with safety cues ($p<.05$, corrected).
Conclusions: These findings provide insight into distributed hippocampal-frontoamygdala circuitry supporting safety learning in humans and suggest potential avenues for interventions that use safety signals to target the biological state of the developing brain during the unique developmental window of adolescence.
Supported By: NIH Director's Early Independence Award; NARSAD Young Investigator Award
Keywords: Anxiety Disorders, Pediatric Anxiety, Amygdala, Fear Learning, fMRI

236. Developing fMRI-Based Biomarkers for Pain and Emotions

Choong-Wan Woo[1]

[1]Center for Neuroimaging Research, IBS

Background: For the last two decades, functional Magnetic Resonance Imaging (fMRI) revolutionized how we study pain, emotions, and their psycho-patho-physiology. However, as evidence accumulates, many of the brain-function mappings from fMRI studies appear to be flawed due to their poor sensitivity, specificity, and reproducibility. A new emerging paradigm, which we termed predictive mapping, has a potential to resolve these issues, building better fMRI-based biomarkers for pain and emotions. This new approach is based on specific uses of machine learning combined with experimental designs optimized for prediction, yielding well-defined neuroimaging signatures of brain-outcome relationships that can be prospectively tested in new individuals, studies, and translational applications.
Methods: In this talk, I will introduce three studies where we used the predictive mapping approach to develop fMRI-based biomarkers for acute ($n = 114$), tonic ($n = 92$), and chronic pain ($n = 72$). I will also talk about an ongoing project where we are developing fMRI markers for positive and negative emotions induced with a novel task, called free association semantic task (FAST).
Results: Our new models showed significant accuracy across multiple datasets (86-100%, all ps $< .05$) in discriminating the target pain and emotions experience from their control conditions, and showed significant correlations in predicting ratings. In addition, the acute pain marker response was reduced by analgesic drug.
Conclusions: These findings highlight how the predictive mapping approach can be effectively used to model different types of pain. It integrates ideas from machine learning, 'big data,' reproducible research, and open science to bring translational goals within reach.
Supported By: IBS
Keywords: Brain Imaging, fMRI, Machine Learning, Biomarkers, Pain, Emotion

237. Frontostriatal Mechanisms of Anhedonia During the Induction and Remission of Depression

Conor Liston[1]

[1]Weill Cornell Medical College

Background: Depression is a fundamentally episodic form of mental illness, yet the neurobiological mechanisms underlying the induction and remission of depressive episodes over time are not well understood. Furthermore, it is unclear how different mechanisms may mediate these processes in subgroups of patients.
Methods: We used resting state fMRI to identify stress-related patterns of altered connectivity associated with distinct subtypes of depression. In a parallel pre-clinical study, we used two-photon microscopy and optogenetic fMRI to investigate how postsynaptic spine remodeling in prefrontal projection neurons contributes to the induction and remission of altered reward-seeking in a rodent chronic stress model.
Results: I will present unpublished results of an on-going effort to optimize neuroimaging biomarkers for diagnosing depression subtypes in human patients and to delineate effects that may be attributable to stress. I will also present unpublished translational data from a rodent chronic stress model showing that the induction of depression-related behavior is associated with clustered, branch-specific spine elimination in prefrontal cortex (N=30 mice, $p<0.0001$). Ketamine reversed these effects by selectively rescuing eliminated spines ($p=0.0012$) and restoring coordinated activity in multicellular ensembles ($p=0.000014$) that predicted motivated escape behavior. Dysfunctional connectivity in frontostriatal circuits suppressed striatal responses to reward-related VTA signals (N=32 runs/6 animals, $p<0.0001$), impairing the expression of reward-seeking behaviors ($p=0.0051$).
Conclusions: These findings implicate antidepressant-induced spine formation in rescuing specific synaptic substrates of stress-related prefrontal circuit dysfunction and in accelerating the remission of anhedonia and other depression-related behaviors. These results may be particularly relevant

for subtypes of depression characterized by altered frontostriatal connectivity and anhedonia.
Supported By: R01 MH109685, Rita Allen Foundation, Dana Foundation, One Mind Institute, Klingenstein-Simons Fellowship in Brain Science
Keywords: Depression, Anhedonia, Dendritic Spines, Two-photon Imaging, Optogenetics

SYMPOSIUM
Exposure to Inflammation and Psychopathology: Transdiagnostic Considerations From the Womb Through Young Adulthood
3:00 p.m. - 5:00 p.m.
Chair: Lauren Ellman

238. Maternal Inflammation During Pregnancy and Offspring Psychopathology: Contributions of Gestational Timing and Fetal Sex

Lauren Ellman[1], Naoise Mac Giollabhui[1], Seth Maxwell[1], Shannon Murphy[1], Lauren Alloy[1], Barbara Cohn[2], Nickilou Krigbaum[2], Piera Cirillo[2], Christian Perez[3], and Elizabeth Breen[3]

[1]Temple University, [2]Child Health and Development Studies, Public Health Institute, [3]University of California, Los Angeles

Background: Evidence suggests that infection during pregnancy is associated with increased risk of offspring psychopathology, such as depression. As most infections do not cross the placenta, maternal immune responses to infection have been considered as potentially contributing to this relationship. The present study sought to determine whether maternal inflammation during pregnancy was related to increased risk of offspring internalizing/externalizing symptoms in childhood and depressive symptoms during adolescence in a prospective, longitudinal birth cohort.
Methods: Participants were 649 pregnant women and their offspring who were continuously followed through adolescence. Markers of maternal inflammation [(interleukin-6 (IL-6), IL-8, IL-1 receptor antagonist (IL-1ra) and soluble TNF receptor (sTNF-RII)] were assayed from archived prenatal sera drawn during the first and second trimesters. Childhood offspring internalizing and externalizing symptoms were assessed via maternal report on questionnaires (offspring ages 9-11) and offspring completed questionnaires for depression symptoms during adolescence (ages 15-17).
Results: Results indicate that 1) increased maternal IL-8 ($p=.004$) and increased maternal IL-6 (approached significance, $p=.085$) was associated with higher levels of externalizing behaviors in offspring and 2) increased maternal IL-1ra ($p=.028$) and increased maternal IL-6 (approached significance, $p=.098$) during the second trimester were associated with higher internalizing behavior. The IL-1ra-internalizing association was significant in female offspring only ($p=.012$). Additionally, higher levels of second trimester maternal IL-6 were associated with significantly higher offspring adolescent depression symptoms ($p=.049$).
Conclusions: This is the first study to determine that gestational timing and fetal sex may be important factors in the associations between maternal inflammation during pregnancy and differential offspring psychiatric outcomes.
Supported By: NIMH R01MH096478
Keywords: Inflammation, Pregnancy, Adolescent Depression, Internalizing Behavior, Externalizing

239. Prenatal Immune Activation Modifies Behavioral Phenotypes Across Multiple Generations

Ulrike Weber-Stadlbauer[1], Juliet Richetto[1], Flavia Mueller[1], and **Urs Meyer**[1]

[1]University of Zurich

Background: Non-genetic transgenerational transmission of behavioral traits has gained increasing recognition in view of its potential importance in the etiology of multifactorial psychiatric disorders. Here, we explored whether maternal immune activation (MIA), which is a known risk factor for various neurodevelopmental and psychiatric disorders, can induce pathological effects across multiple generations.
Methods: We used an established MIA model that is based on maternal exposure to the viral mimetic poly(I:C) in mice (C57BL6/N). First-generation (F1) MIA offspring and control offspring were either assigned to behavioral testing when they reached adult age, or they were used as breeders to obtain second- (F2) and third- (F3) generation offspring. Adult F2 and F3 offspring were then also assigned to behavioral testing.
Results: Compared to F1 control offspring ($n=26$), F1 MIA offspring ($n=21$) showed a number of behavioral abnormalities, including reduced sociability in the social interaction test ($p<0.001$), impaired sensorimotor gating in the prepulse inhibition test ($p<0.01$), and increased sensitivity to the dopamine-stimulating drug, amphetamine ($p<0.05$). While F2 ($n=18$) and F3 ($n = 10$) offspring of MIA-exposed ancestors similarly showed deficits in sociability ($p<0.05$), they developed novel phenotypes that were not seen in F1 MIA offspring, including blunted amphetamine sensitivity ($p<0.05$), behavioral despair in the forced swimming test ($p<0.05$), and anhedonia in the sucrose preference test ($p<0.05$).
Conclusions: Prenatal immune activation leads to a modification of pathological phenotypes across generations. While the spectrum of behavioral abnormalities emerging in F1 MIA offspring recapitulates “psychosis-like” phenotypes, their subsequent generations develop “depression-like” phenotypes that were initially not present in the F1 generation.
Supported By: Swiss National Science Foundation (grant 310030_169544)
Keywords: Maternal Immune Activation, Inflammation, Schizophrenia, Depression, Epigenetic

240. Extracellular Free Water and Glutathione in First Episode Schizophrenia and a Non-Human Primate Model of Maternal Immune Activation – Exploring Neuroimmune Mechanisms of Psychiatric Disorders

Tyler Lesh[1], Costin Tanase[1], Huan Wang[1], Erika Steinbauer[1], Jeffrey Bennett[1], Ana-Maria Iosif[1], Judy Van de Water[1], Richard J. Maddock[1], J. Daniel Ragland[1], Tara A. Niendam[1], Martin Styner[2], David Amaral[1], Melissa Bauman[1], and Cameron S. Carter[1]

[1]University of California, Davis, [2]University of North Carolina, Chapel Hill

Background: Recent work highlights an immune-based component of psychiatric disorder etiology, particularly schizophrenia. We evaluated two putative biomarkers of neuroinflammation—diffusion MRI free water (FW) and 1H-MRS Glutathione (GSH)—in a first episode schizophrenia (SZ) sample. Furthermore, we developed a non-human primate (NHP) model of maternal immune activation (MIA) to test that maternal immune response contributes to parallel brain changes in developing NHP offspring.
Methods: The human study consisted of thirty-six SZ participants and forty age/gender-matched controls (HC). The NHP study consisted of fourteen pregnant rhesus monkeys who received polyICLC and fourteen pregnant control monkeys. All subjects underwent parallel multi-shell diffusion MRI and 1H-MRS GSH-optimized MEGA-PRESS scans (Siemens 3T). Human data were collected within two years of psychosis onset and NHP data were collected longitudinally (6-month data currently presented).
Results: SZ participants demonstrated significantly elevated FW in whole-brain gray ($p<.05$) with no difference in white matter ($p=.06$) versus HC. There was a significant negative correlation between DLPFC GSH and both gray and white matter FW in SZ ($r=-.44$ and $-.37$, respectively; both $p<.05$). While 6-month-old MIA-exposed rhesus offspring showed no whole-brain gray/white matter FW increase (both $p>.09$), frontal gray FW was elevated ($p=.013$). GSH levels did not differ in any comparison (all $p > .2$).
Conclusions: These data provide compelling convergent evidence for the presence of neuroinflammatory processes in SZ, particularly given the inverse relationship between GSH and FW. Prefrontal gray matter FW increases in MIA-exposed NHP offspring complement the human schizophrenia literature and provide a more mechanistic understanding of neuroimmune involvement in psychiatric disorders.
Supported By: P50MH106438
Keywords: Extracellular Free Water, Glutathione, First Episode Schizophrenia, Non-human Primates, Neuroinflammation

241. Risk for Bipolar Spectrum Disorders and Associations Between Inflammation and Reward-Related Brain Function

Lauren Alloy[1], Iris Chat[2], Daniel Moriarity[1], Gregory Miller[2], and Robin Nusslock[2]

[1]Temple University, [2]Northwestern University

Background: Reward hypersensitivity increases risk for first onset and recurrences of bipolar spectrum disorders (BSDs), and individuals with BSDs exhibit elevated proinflammatory cytokines in manic, euthymic, and depressed states. Some recent studies find that inflammation is associated with elevated reward responsiveness when potential reward probability or magnitude is high.
Methods: We examined associations between inflammatory biomarkers and self-report and neural measures of reward sensitivity in 107 emerging adults in one of three groups based on self-reports of reward sensitivity and lifetime diagnostic interview: moderate reward sensitivity (MR), high reward sensitivity (HR) without a BSD, and high reward sensitivity with a BSD (HR+BSD). Participants completed an fMRI scan with the monetary incentive delay (MID) task to assess neural reward responses and a blood draw, assayed for interleukin-6, IL-8, IL-10, and tumor necrosis factor alpha (TNFα).
Results: The HR and HR+BSD groups exhibited higher IL-6 (and IL-6, IL-10 composite) than the MR group, controlling for age, sex, and BMI ($F=4.843, p<.01$; total $N = 107$). In addition, controlling for age, sex, BMI, and group status, greater inflammation (IL-6, IL-8, IL-10, TNFα composite) was significantly correlated ($r=.31, p<.01$) with elevated bilateral orbitofrontal cortex (OFC) activation to anticipation of rewards in the MID task, particularly for high magnitude rewards ($r=.34$). Finally, the Group x IL-6 interaction predicted bilateral OFC activation to reward anticipation ($F=8.34, p<.01$), such that high reward sensitivity (HR and HR+BSD combined) participants with high IL-6 levels exhibited the greatest elevated OFC activation to reward anticipation.
Conclusions: Thus, elevated reward responsiveness and inflammation may be joint vulnerabilities for BSDs.
Supported By: NIMH R01 MH077908 and NIMH R01 MH102310
Keywords: Bipolar Disorder, Reward Sensitivity, Inflammation, Orbitofrontal Cortex

SYMPOSIUM
Two Markers of Neurodevelopmental Disorders: Behavioral Microanalysis and Neuroimaging

3:00 p.m. - 5:00 p.m.
Chair: Daniel Pine
Co-Chair: Amy Margolis

242. An Early Behavioral Index of ASD From Automated Microanalysis of Movement Dynamics

Katherine Martin[1], Zakia Hammal[2], Jeff Cohn[3], and **Daniel Messinger**[4]

[1]Tobii Pro, [2]The Robotics Institute, Carnegie Mellon University, [3]University of Pittsburgh, [4]University of Miami

Background: Symptoms of ASD may alter the coordination infant-parent interactions, disrupting successful communication and social interactions. Previous research indicated that six-month-old infants with later ASD did showed no reduction in smiling following parental unresponsiveness (the still-face

effect). Using automated tracking, we recently found that older children with and without ASD systematically differ in their head movements to social stimuli. In this study, we employed microanalytic, automated measurement to examine head movement coordination between infants and parents.
Methods: Infant-parent dyads (N=64) were video-recorded during the Face-to-Face/Still-Face at 6 months. Angular displacement and velocity of infants' and parents' pitch, yaw, and roll were quantified from the video-recordings using a computer-vision approach. We assessed differences in head movement coordination between infants and parents in high-risk children with (High-Risk/ASD, n=10) and without (High-Risk/No-ASD, n=22) ASD, and low-risk children (Low-Risk/No-ASD, n=22).
Results: R-to-Z transformations revealed that the correlations of the angular velocity of the pitch, yaw, and roll between infant and parent head movement were higher in the High-Risk/ASD group than the High-Risk/No-ASD and the Low-Risk/ASD group (ps<.05).
Conclusions: Here, automated measures of early interaction revealed that infants with later ASD had the highest levels of coordination with their parents in the velocity of head movement. Parents of High-Risk/ASD infants may match their infants' movements more vigilantly than other parents. Previous research indicated that older children with ASD exhibited exaggerated head movement to social stimuli. The findings support the importance of movement atypicalities in ASD and suggest that they warrant further exploration as potential biomarkers.
Supported By: 1R01GM105004
Keywords: Infancy, Behavioral Biomarkers, Interaction, Autism Spectrum Disorder

243. Profiling Infants' Communicative Behavior: Identifying Behavioral Markers of Infant Difficult Temperament and Insecure Attachment

Amy Margolis[1], Sang Han Lee[2], and Beatrice Beebe[1]

[1]Columbia University Medical Center, [2]Nathan Kline Institute

Background: Face-to-face play elicits the infant's most advanced communication capacities at 4 months of age. Prior findings suggest that infant self-contingency, the degree of stability/variability of the infant's behavior from moment-to-moment, is associated with infant temperament and attachment. Herein we assessed whether infant self-contingency of communicative behavior would cohere into clusters of infants and associate with psychosocial measures of infant temperament and attachment.
Methods: 132 mother-infant videotaped interactions from a community sample were coded on a 1-second time-base with 4 modalities of infant communication behaviors (gaze, facial affect, vocal affect, head orientation). K-means clustering classified infants based on variation in predictability of the infant's moment-by-moment behaviors (the autocorrelation function of a behavioral time-series) and degree of display of behaviors (intercept of the time-series); clusters were tested for association with infant temperament and attachment (Fisher's Least Significance Difference).
Results: Five of 10 clusters associated with outcomes (all $p < .05$, corrected for multiple comparisons). One cluster ($N = 14$) represented an extremely distressed baby, with high predictability of negative facial and vocal affect combined with orientational agitation, and the highest degree of disorganized attachment. One cluster represented an 'inscrutable' infant (N=13), looking away, oriented away, silent, and facially uncommunicative, and had the highest maternal ratings of difficult temperament. Three clusters showed patterns of high orientational aversion or silence ($N = 18, 7, 15$) that differentiated psychosocial outcomes of attachment resistance.
Conclusions: These 4-month behavioral profiles may function as markers of later psychosocial difficulties, thereby providing targets for dyadic-behavioral treatment as early as 4-months of age.
Supported By: NIEHS, The NVLD Project
Keywords: Infant Temperament, Infant Attachment, Video Microanalysis

244. Behavioral Inhibition, Anxiety, and the Neural Correlates of Cognitive Control

Lauren White[1], Nathan Fox[2], and Daniel Pine[3]

[1]Children's Hospital of Philadelphia, [2]University of Maryland, [3]National Institute of Mental Health

Background: Behavioral Inhibition (BI) is an early identified temperament characterized by increased fear of unfamiliar people and situations. Children identified as behaviorally inhibited in toddlerhood are at increased risk for anxiety disorders in adolescence and adulthood. Thus, it is important to understand the factors that may increase or decrease the link between BI and later anxiety problems. The current study examined how neural correlates underlying cognitive control moderate this developmental link.
Methods: A total of 64 adolescents (Mean=13.07 years, SD=0.7), who were previously assessed on behavioral inhibition during toddlerhood, completed a cognitive control task (i.e., the flanker task) during fMRI acquisition. Multivariate modeling fMRI analyses were conducted to examine relations between early identified BI and neural correlates of cognitive control in adolescents. Interactions between BI, anxiety, and brain function were also examined.
Results: Imaging analyses ($p < .005$, whole brain corrected) showed that in a group of adolescents, toddlerhood BI was associated with decreased recruitment of the dorsolateral PFC and inferior parietal cortex during trials requiring greater levels of cognitive control. Interactions also emerged between BI, brain function, and concurrent anxiety in several regions (e.g., medial frontal cortex, inferior parietal cortex). These interactions suggest that aberrant brain activation underlying cognitive control may moderate the link between early-identified temperament and anxiety problems in adolescents.
Conclusions: Early identified temperament was associated with a distinct pattern of brain function during a cognitive control task 10 years later. Moreover, aberrant brain function

underlying cognitive control may be a risk factor for children with BI.
Supported By: NIH R01
Keywords: Anxious Temperament, Anxiety, Cognitive Control, Behavioral Inhibition

245. Brain Signal Variability as a Novel Marker of Flexible Behavior in Autism

Lucina Uddin[1] and Jason Nomi[1]

[1]University of Miami

Background: Autism spectrum disorder (ASD) is characterized by executive function deficits, the nature of which are incompletely understood. Brain signal variability has previously been linked to flexible cognition and behavior, however no studies have used this neuroimaging marker to investigate the neurobiology of ASD. Here we examine the relationship between brain signal variability and flexible behavior in ASD for the first time.
Methods: We quantified brain signal variability using a measure called mean square successive difference (MSSD) applied to resting state fMRI data collected from participants with ASD and typically developing (TD) individuals made available through the Autism Brain Imaging Data Exchange (ABIDE NYU site; ASD n = 57; 8-39 years old and TD n = 67; 7-30 years old). We used scores on the restricted and repetitive behavior subscale of the Autism Diagnostic Interview-Revised (ADI-R) as indices of flexible behavior in ASD.
Results: Significant clusters ($p < 0.05$ GRF corrected) demonstrating unique developmental trajectories of brain signal variability between ASD and TD were identified in brain areas including frontal, temporal, occipital/parietal, and cerebellar regions. MSSD values were averaged over voxels in each cluster and were contrasted alongside behavioral measures (ADI-R) in ASD using partial correlations controlling for age ($p < 0.05$). Significant relationships emerged between atypical MSSD in ASD and ADI-R scores such that those with greater symptom severity showed higher MSSD in lateral occipital/parietal areas.
Conclusions: Individuals with ASD exhibit unique developmental trajectories of brain signal variability compared with TD individuals, which may underlie symptom severity in the domain of flexible behaviors.
Supported By: This work was supported by awards K01MH092288 and R01MH107549 from the National Institute of Mental Health, a Slifka/Ritvo Innovation in Autism Research Award, and a NARSAD Young Investigator Grant to L.Q.U.
Keywords: Autism Spectrum Disorder, Brain Connectivity, Machine Learning, Magnetic Resonance Imaging (MRI)

SYMPOSIUM
Neuroimaging Biomarkers of Illness Onset and Treatment Response in Bipolar Disorder and Schizophrenia

3:00 p.m. - 5:00 p.m.
Chair: Allan Young
Co-Chair: Sameer Jauhar

246. Neuroimaging Markers of Risk and Resilience to Bipolar Disorder

Sophia Frangou[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Bipolar disorder (BD) is a heritable disorder characterized by mood dysregulation associated with brain functional dysconnectivity. Prior research has focused on the detection of risk- and disease-associated dysconnectivity in individuals with BD and their first-degree relatives. The current study takes a complementary approach that seeks to identify adaptive brain features associated with avoidance or delayed illness onset in unaffected relatives of patients with BD.
Methods: Comparison of patients with bipolar disorder to their unaffected relatives and healthy individuals from 2 independent samples based on neuroimaging features derived from structural, task- related and head-motion corrected resting-state functional data.
Results: Familial vulnerability to bipolar disorder was associated with (a) increased insular volume, (b) abnormal functional connectivity of the ventrolateral prefrontal cortex during tasks of response inhibition and emotional processing and (c) abnormal resting-state connectivity of the sensorimotor network. Brain imaging markers of resilience comprised (a) increased volume of the vermis, (b) increased connectivity of the dorsal and ventrolateral prefrontal cortex during response inhibition and (c) increased integration of the default mode network.
Conclusions: These findings indicate the presence of neural mechanisms that may promote resilience, or at least delay the onset of bipolar disorder. Further studies are needed to chart the longitudinal course of these potentially protective connectivity features and determine the causal mechanisms involved.
Supported By: National Institutes of Health (R01-MH104284-01A1)
Keywords: Bipolar Disorder-I, Multimodal Neuroimaging, Resilience and Vulnerable

247. Imaging the Distribution and Effects of Lithium in the Brain in Bipolar Disorder

David Cousins[1], Fiona Smith[1], Joe Necus[1], Peter Thelwall[1], Carly Flowers[1], Peter Taylor[1], Nishant Sinha[1], Yujiang Wang[1], and Andrew Blamire[1]

[1]Newcastle University

Background: Lithium is thought to improve white matter (WM) integrity in bipolar disorder (BD) because diffusion weighted imaging shows higher fractional anisotropy (FA) values in those taking the drug. Interpretation of this observation would be aided by tissue-level determination of brain lithium concentration. In vivo lithium magnetic resonance spectroscopy (7Li-MRS) requires long acquisition times but as 7Li yields a spectral singlet, advanced magnetic resonance imaging (MRI) techniques can be applied.

Methods: A highly efficient and novel balanced steady-state free precession 7Li-MRI technique was developed on a clinical 3T scanner (scan duration 8 minutes), and evaluated in test objects and patients. Euthymic lithium-treated and lithium-naïve BD patients also underwent diffusion weighted imaging. A voxel-wise estimation of generalised fractional anisotropy (gFA) was performed and values within WM regions of interest (ROI) compared between treatment groups. The relationship between 7Li-MRI signal intensity and gFA differences was explored.
Results: 7Li-MRI signal intensity was uniform across uniform test objects and closely correlated with concentration (Pearson coefficient 0.98). In lithium-treated patients, brain lithium distribution was heterogeneous (coefficient of variation 27.9±3.6%; scan evaluation subgroup n=8) and greater in WM compared to grey matter (6.10±0.89 versus 5.22±0.47; arbitrary units, p=0.03). Comparing patient groups, those taking lithium (n=10) had higher gFA in 41 of the 48 WM ROI than lithium-naïve patients (n=16). 7Li-MRI signal intensity correlated positively with gFA effect size (r=0.45; p=0.001).
Conclusions: Brain lithium distribution can be swiftly measured using 7Li-MRI. Regional lithium concentration correlated with localised tissue-level effects, strengthening the assertion that lithium improves WM integrity.
Supported By: Medical Research Council UK (Clinician Scientist Fellowship BH135495 to Dr D Cousins)
Keywords: Lithium, Magnetic Resonance Imaging, Bipolar Disorder, Diffusion Tensor Imaging (DTI)

248. Neuroimaging Biomarkers Predicting Disorder in Those at High Familial Risk of Schizophrenia or Bipolar Disorder

Stephen Lawrie[1], Heather Whalley[1], and Andrew McIntosh[1]

[1]University of Edinburgh

Background: Schizophrenia (SCH) and Bipolar disorder (BPD) share some risk factors, clinical and biological features but not others. Understanding these differences may help differentiate disorders at an earlier stage and facilitate more effective treatment.
Methods: We have prospectively examined cohorts of >100 people at high familial risk of schizophrenia, high familial risk of bipolar disorder, and healthy controls, over more than 10 years, with a range of behavioural, cognitive, and neuroimaging measures.
Results: At baseline, the SCH high risk group had more psychotic symptoms, schizotypal features and memory impairment than controls, while the BPD high risk group had more depression and cyclothymia. The groups showed markedly different fMRI activations on a sentence completion task (reduced fronto-thalamic versus increased amygdala activation, both correlated with increased cumulative genetic loading for the respective disorder).

Those baseline differences were weak predictors of schizophrenia, as were cortical folding and surface area. The strongest predictors of SCH were reduced (para)hippocampal volume and increased parietal activation; but machine learning analysis overall predictive accuracy with a single sMRI scan was 94% (and 74& in an independent cohort). In the BPD risk group, those who developed MDD had more depression/anxiety, early life stress and decreased cognitive flexibility, reduced parahippocampal thickness and increased insula/prefrontal activation versus those who did not.
Conclusions: In populations at high familial risk of schizophrenia or bipolar disorder, both trait markers of risk and predictive of disorder biomarkers are quite distinct. There may be some overlapping liability to psychosis in general. Early developmental abnormalities may be relatively specific to schizophrenia.
Supported By: MRC, Health Foundation, Sackler Foundation
Keywords: Schizophrenia, Bipolar Disorder, High Familial Risk, Functional Neuroimaging, Structural Neuroimaging

249. Dopaminergic and Glutamatergic Function in Bipolar Disorder and Schizophrenia and Treatment Response: PET and MRS Evidence in Drug Naive Patients

Oliver Howes[1], Matthew Nour[2], Fiona Pepper[2], and Sameer Jauhar[3]

[1]MRC LMS Hammersmith Hospital and King's College London, [2]MRC LMS and KCL, [3]King's College London

Background: Understanding the neurobiology underlying psychosis across diagnoses and in treatment response is important to help guide the development of new treatments and biomarkers for treatment response. Elevated dopamine synthesis capacity and glutamate levels have been associated with schizophrenia, but it remains unknown how they compare across psychotic disorders or relate to treatment response.
Methods: Two cohorts of first episode patients, one with a diagnosis of schizophrenia (n=16) and another with a diagnosis of bipolar affective disorder (n=22) received 18F-DOPA PET and [1H]-MR spectroscopy imaging and clinical measures. All patients had experienced a psychotic episode. Patients went on to standard antipsychotic treatment and received clinical measures and repeat imaging after ~6 weeks of treatment at a therapeutic dose.
Results: Striatal dopamine synthesis capacity (Kicer) was significantly elevated in both bipolar (effect size=1.02; p<0.003) and schizophrenia (effect size=0.9; p<0.05) groups, compared to controls. There was no significant difference in dopamine synthesis capacity between bipolar and schizophrenia groups (p>0.4). Kicer was significantly positively correlated with positive psychotic symptom severity in the transdiagnostic group of people with psychosis (r=0.52, p<0.004). There were no differences in glutamate levels in the anterior cingulate cortex.

There was a positive relationship between baseline dopamine synthesis and subsequent response to treatment (r=0.5, p<0.05) and dopamine synthesis capacity was significantly elevated in treatment responders relative to treatment non-responders (p<0.05).
Conclusions: Elevated dopamine synthesis capacity is associated with psychosis across diagnostic boundaries and linked

to the severity of psychotic symptoms, even after adjusting for manic symptom severity, and treatment response.
Supported By: MRC UK MC-A656-5QD30
Keywords: Bipolar Disorder, Schizophrenia, Treatment, Etiology

SYMPOSIUM
A Multi-Modal, Translational Examination of Striatal Dopamine and Motivation in Depression
3:00 p.m. - 5:00 p.m.
Chair: Franklin Schneier

250. Anergia and Effort-Related Aspects of Motivational Dysfunction in Animal Models of Depressive Symptoms: The Role of Mesolimbic Dopamine and Related Circuitry

John Salamone[1], Merce Correa[2], Samantha Yohn[3], Renee Rotolo[1], Jen-Hau Yang[1], and Rose Presby[1]

[1]University of Connecticut, [2]University of Jaume I, [3]Vanderbilt University

Background: Motivational symptoms such as anergia, psychomotor retardation, or apathy are common in depression and other disorders. Many depressed people lack behavioral activation, and show reduced selection of high-effort activities. Effort-based choice tasks have been developed as animal models of motivational symptoms. In rodents, these tasks allow animals to choose between a more valued reinforcer obtained by high-effort actions versus a low-effort/low-reward option. Dopamine (DA) antagonism and mesolimbic DA depletions shift decision-making, decreasing selection of the high-effort option and increasing choice of the low effort alternative, under conditions that do not affect reward preference, appetite, or hedonic reactivity.
Methods: A low-effort bias in rodents is induced by conditions associated with depressive symptoms, including injections of tetrabenazine (TBZ), which blocks monoamine storage, and pro-inflammatory cytokines (IL-1B, IL-6).
Results: Several DA uptake inhibitors can reverse the effort-related effects of TBZ or cytokines (bupropion, GBR12909, methylphenidate, modafinil, lisdexamfetamine, and others; ANOVA, $n>8$; $p<0.05$). The norepinephrine (NE) uptake blocker desipramine does not reverse the effects of TBZ, nor do serotonin uptake blockers (fluoxetine, S-citalopram). The lack of effect of SSRIs is consistent with reports showing that SSRIs are relatively ineffective for treating fatigue and anergia. Furthermore, injections of DA uptake blockers increased progressive ratio work output, while fluoxetine, desipramine, and atomoxetine did not. Bupropion and GBR12909 at behaviorally active doses elevated extracellular DA in accumbens as measured by microdialysis, while fluoxetine, desipramine and atomoxetine did not.
Conclusions: Effort-related motivational symptoms can be modeled in rodents, and these studies illustrate a key role for DA in regulating these functions.

Supported By: NIH/NIMH; Shire; Prexa
Keywords: Depression, Motivation, Anergia, Fatigue, Accumbens

251. Dopamine Release in Treatment-Naïve Major Depressive Disorder: A [11C]-(+)-PHNO Positron Emission Tomography Study

Franklin Schneier[1], Mark Slifstein[2], Alexis Whitton[3], Diego Pizzagalli[3], Jenna Reinen[4], Patrick McGrath[5], Dan Iosifescu[6], and Anissa Abi-Dargham[2]

[1]NY State Psychiatric Institute, [2]Stony Brook University, [3]Harvard Medical School/McLean Hospital, [4]Yale University, [5]Columbia University, [6]Nathan Kline Institute for Clinical Research

Background: Major depressive disorder (MDD) and anhedonia have been associated with mesolimbic dopamine (DA) system dysfunction, but neuroimaging studies using nonselective D2/D3 antagonist radioligands have yielded mixed results. The current study used [11C]-(+)-PHNO, an agonist radioligand with preferential selectivity for D3 over D2 receptors and high sensitivity to the DA-releasing effects of amphetamine, to examine DA function in MDD.
Methods: Twenty medication-naïve adults with MDD, and 20 comparison subjects completed [11C]-(+)-PHNO PET before and after oral dextroamphetamine. MDD participants were subsequently treated for 6 weeks with the DA agonist pramipexole
Results: Baseline binding potential (BPND) and percent reduction post-amphetamine (ΔBPND) did not differ between groups across all regions of interest (BPND $p = .48$; ΔBPND $p = .19$) or for any single region. There was a trend for greater DA release in MDD in the ventral striatum (-34% vs. -30%, $p = .072$, $d = .58$). The MDD group evidenced significant improvement of depression ($p < .001$) and anhedonia ($p < .001$) with pramipexole treatment, but BPND and ΔBPND were not associated with baseline severity, clinical response, or BOLD response to reward prediction error.
Conclusions: These largely negative results contrast with evidence (presented separately) from the same sample showing group differences in striatal reward prediction error and behavioral reward learning, both of which have been previously associated with DA function. Limitations of this study include the small sample size, multiple factors potentially contributing to BPND, and the limitations of amphetamine-induced DA release as a model for physiological DA release.
Supported By: NIMH grant 5R01MH099322
Keywords: PET, Major Depression, Dopamine, [11C]-(+)-PHNO, Amphetamine Challenge

252. Major Depressive Disorder is Associated With Blunted Learning Signals in Medial Prefrontal Cortex and Putamen When Seeking Monetary Reward

Jenna Reinen[1], Alexis Whitton[2], Diego Pizzagalli[2], Mark Silfstein[3], Anissa Abi-Dargham[3], Patrick McGrath[4], Dan V. Iosifescu[5], and Franklin Schneier[6]

[1]Yale University, [2]Harvard Medical School/McLean Hospital, [3]Stony Brook University, [4]New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, [5]NYU Langone Medical Center, Nathan Kline Institute for Psychiatric Research, [6]Columbia University & New York State Psychiatric Institute

Background: Debate exists whether the motivational symptoms of major depressive disorder (MDD) are related to abnormal dopamine-supported reinforcement learning processes in the striatum. We hypothesized that regions of interest in the cortico-striatal pathway would demonstrate blunted responses to a learning signal, prediction error (PE), in persons with MDD, and association with anhedonia.
Methods: Medication-naive MDD patients (n=24) and controls (n=24) completed a probabilistic reinforcement learning task involving two conditions during fMRI. Participants learned to choose: (a) the cue associated (70%) with a monetary gain, and (b) the cue associated (70%) with avoidance of monetary loss. Responses were examined across three stages: choice, feedback, and reinforcement outcome. A Q-learning model was used to generate behavioral learning metrics and trial-specific PE regressors for the imaging analyses.
Results: In the gain condition, imaging results revealed significant group differences in response to signed PE (controls>MDD) in medial prefrontal cortex (mPFC) during feedback, and in bilateral putamen during outcome (FWE corrected at $p<0.05$). In the loss condition, no group differences survived correction, though we found a relationship between response to PE in putamen and severity of anhedonia ($r=-0.61$, $p<0.01$). Behavioral effects did not differ between groups, but optimal choice performance in the loss condition was correlated with severity of anhedonia ($r=0.42$, $p=0.04$).
Conclusions: Patients with MDD showed blunted gain-related learning signals in mPFC during feedback and in putamen during reinforcement outcome. Anhedonic symptoms were associated with performance and putamen response in the loss condition. These findings implicate cortico-striatal dysfunction in depression and symptoms of anhedonia.
Supported By: NIMH grant 5R01MH099322
Keywords: Depression, Reinforcement Learning, Striatum, Medial Prefrontal Cortex, Anhedonia

253. Utilizing a Behavioral Assay of Reward Learning to Predict Clinical Response to a Dopamine Agonist in Individuals With Depression

Alexis Whitton[1], Jenna Reinen[2], Mark Slifstein[3], Patrick McGrath[4], Dan Iosifescu[5], Anissa Abi-Dargham[3], Diego Pizzagalli[1], and Franklin Schneier[6]

[1]Harvard Medical School & McLean Hospital, [2]Yale University, [3]Stony Brook University, [4]New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, [5]NYU Langone Medical Center, Icahn School of Medicine at Mount Sinai, [6]Columbia University & New York State Psychiatric Institute

Background: The efficacy of dopamine (DA) agonists in treating major depressive disorder (MDD) has been tied to their effects on mesolimbic DA and reward function. However, individual responses vary, and an important question is whether DA agonists are most beneficial for depressed individuals with reward-based deficits. This study evaluated whether a behavioral measure of reward learning would predict response to the D3-preferring DA agonist pramipexole (PPX).
Methods: Medication-naïve individuals with MDD (n=26) and healthy controls (n=26) performed a probabilistic reward learning task (PRT) that used an asymmetrical reinforcement schedule to assess behavioral response bias. MDD individuals completed a counterbalanced version of the PRT again following six weeks of treatment with PPX. Depressive and anhedonic symptoms were monitored weekly.
Results: A Group (controls, MDD) x Block (1,2,3) ANOVA revealed a main effect of Group for baseline response bias, $F(1,40)=8.71$, $p=0.005$, $\eta p2=0.18$, with the MDD group exhibiting lower response bias relative to controls. Contrary to hypotheses, response bias did not change following treatment ($p=0.49$); however, baseline response bias predicted changes in depression ($\beta=-2.61$, $p=0.002$), and anhedonia severity ($\beta=-1.96$, $p=0.007$). Unexpectedly, symptom improvement was greater in individuals with more intact reward learning.
Conclusions: These findings suggest that clinical response to the DA agonist PPX is greater in MDD individuals who have more preserved reward learning – a measure linked to phasic DA signaling and integrity of frontostriatal pathways. The implication of these findings for the use of dopaminergic medications in depression will be discussed in the context of PPX's putative effects on tonic DA and motivation.
Supported By: NIMH grant 5R01MH099322
Keywords: Depression, Dopamine, Reward Learning, Antidepressant Medication, Frontostriatal Circuits

SYMPOSIUM
Mechanisms of Deregulated Balance of Glutamatergic Excitation and GABAergic Inhibition: Implications for Cognitive and Mood Symptoms in Psychiatric Disorders

3:00 p.m. - 5:00 p.m.
Chair: Etienne Sibille

254. Dissociable Contributions by Prefrontal Cortical Gaba and Glutamate Transmission in Regulating Executive and Affective Functions Relevant to Schizophrenia

Stan Floresco[1]

[1]University of British Columbia

Background: Evidence from humans and animal models suggest that schizophrenia is associated with perturbed GABA and glutamate transmission in the prefrontal cortex (PFC). Dysfunction within these systems may underlie cognitive abnormalities associated with the disorder. What remains unclear is how diminished inhibitory vs excitatory transmission

differentially contribute to impairments across domains of cognition affected in schizophrenia.
Methods: We used a battery of preclinical translationally-relevant assays to compare/contrast how pharmacological reduction of inhibitory GABA-A transmission or excitatory transmission within the rat PFC alters cognitive/emotional functioning
Results: Reducing PFC GABA (but not NMDA) activity increased "false alarm" responding during sustained attention ($n=18;p<0.05$). Performance of a paired-associates task was also impaired by reduced GABAergic (but not NMDA) signaling ($n=7;p<0.001$). PFC GABA and NMDA antagonism induced delay-independent vs dependent working memory deficits, respectively (ns=9-13; $p<0.01$); the former more closely resembling what is observed in schizophrenia. Targeting PFC GABA impaired spatial reference/working memory, and molecular analyses revealed these effects were associated with aberrant activation of downstream nuclei, including the hippocampus (ns=6-8, $p<0.01$). PFC disinhibition increased fear to a neutral stimulus and reduced fear to an aversive one ($ns=12-13;p<0.01$), an effect nearly identical to that observed in schizophrenia.
Conclusions: Reducing PFC GABA induces numerous cognitive/affective abnormalities that are qualitatively similar to disturbances in schizophrenia. These effects are distinct from those caused by reduced excitatory transmission. These results provide novel insight into how imbalance in inhibitory vs excitatory transmission underlies cognitive/emotional abnormalities, and suggests that perturbed GABA transmission may be a major contributing factor to these symptoms of schizophrenia.
Supported By: Canadian Institutes of Health Research
Keywords: GABA, Prefrontal Cortex, NMDA Antagonists, Cognition, Salience

255. Chemicogenetic Restoration of the Prefrontal Cortex to Amygdala Pathway Ameliorates Stress-Induced Deficits

Zhen Yan[1]

[1]State University of New York at Buffalo

Background: Corticosteroid stress hormones exert a profound impact on cognitive and emotional processes. Understanding the neuronal circuits that are altered by chronic stress is important for counteracting the detrimental effects of stress in a brain region- and cell type-specific manner.
Methods: Using the chemogenetic tool, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), which enables the remote, non-invasive and long-lasting modulation of cellular activity and signal transduction in discrete neuronal populations in vivo, we sought to identify the specific neuronal circuits and cell populations that mediate the multifaceted responses to chronic stress. Young male SD rats were used, $n=8$-10 rats for each group, $p<0.05$.
Results: We found that prolonged severe stress induced the diminished glutamatergic projection from pyramidal neurons in prefrontal cortex (PFC) to GABAergic interneurons in basolateral amygdala (BLA), leading to the loss of feedforward inhibition and ensuing hyperexcitability of BLA principal neurons, which caused a variety of behavioral abnormalities. Activating PFC pyramidal neurons with hM3D(Gq) DREADD restored the functional connection between PFC and BLA in stressed animals, resulting in the rescue of recognition memory, normalization of locomotor activity and reduction of aggressive behaviors. Inhibiting BLA principal neurons directly with hM4D(Gi) DREADD also blocked BLA hyperactivity and aggressive behaviors in stressed animals.
Conclusions: The chemogenetic approach has offered a novel avenue to counteract the stress-induced disruption of circuitry homeostasis. It provides insights for discovering the effective treatment of stress-related mental disorders associated with PFC network dysfunction.
Supported By: R01-MH108842
Keywords: Corticosteroid Stress Hormones, Designer Receptors Exclusively Activated by Designer Drugs, Prefrontal Cortex, Amygdala, GABAergic Interneurons

256. Targeting GABAergic SST-Positive Interneurons Deficits: Implications for Cognitive and Mood Symptoms in Depression and Other Brain Disorders

Etienne Sibille[1]

[1]University of Toronto - CAMH

Background: The brain excitation inhibition balance (EIB) is characteristically disrupted in neuropsychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BPD), anxiety disorders, and schizophrenia (SCZ). Nearly three decades of research demonstrate a role for reduced GABA level and function in altered EIB. In MDD, recent evidence from human postmortem and animal studies suggests a selective vulnerability of GABAergic interneurons that co-express the neuropeptide somatostatin (SST).
Methods: To investigate the EIB in MDD, we used human post-mortem samples and genetic rodent models, combined with genomic and bioinformatics approaches. To target deficient GABAergic function, we used medicinal chemistry, pharmacological approaches and rodent behavioral models.
Results: We reported consistent reductions of SST and other markers of GABAergic neurons targeting pyramidal cell dendrites in post-mortem samples of MDD patients. We and others have extended these findings to BPD, SCZ and Alzheimer's disease (AD). Our rodent studies demonstrate that reduced SST+ cell induces changes in behavioural emotionality.

Novel small molecule compounds with positive allosteric modulation at the alpha5-containing GABA-A receptor, which partly mediate the function of SST+ neurons, now show dose-dependent robust precognitive and antidepressant effects. Results have been confirmed using series of related compounds (adult C57B6 mice; $n=8$-10/group/dose, 50% female; alpha=0.05).
Conclusions: Reduced SST expression and SST-positive cell function is frequently observed in MDD and other brain disorders, suggesting a selective vulnerability of these cells and a deficit in regulating excitatory input onto pyramidal neurons. Targeting these deficits through augmenting GABA function at receptors mediating SST cell function has procognitive and antidepressant potential.

Supported By: CHIR, NARSAD
Keywords: Depression, Antidepressant, Cognition, Drug Development, Pre-Clinical

257. Differential Hippocampal and Prefrontal Cortical E/I Imbalances Related to GABAA Dysfunction Contribute to the Subchronic Phencyclidine-Induced Deficits in Mouse Memory, Social Interaction and Psychosis Readout

Herbert Meltzer[1], Masanori Miyauchi[2], Lakshmi Rajagopal[1], Nichole Neugebauer[1], and Mei Huang[1]

[1]Northwestern Feinberg School of Medicine, [2]Dainippon Sumitomo, Northwestern University

Background: Schizophrenia (SCH) is characterized by deficits in cognition, reality testing, and social interaction (SI), with E/I imbalance a likely cause. Subchronic (sc) administration of phencyclidine (PCP) models these deficits in rodents.
Methods: We assessed multiple types of GABAergic drugs alone, and combined with the atypical antipsychotic drug, lurasidone (LUR), on novel object recognition (NOR), reversal learning (RL), SI, and acute PCP-induced locomotor activity (LMA) in control C57Bl6 and scPCP-treated mice following withdrawal of scPCP, administration of bicuculline (BIC), a weaker GABAA antagonist, in to PFC and HIP, and invivo microdialysis in awake freely moving mice to assess PFC and hippocampal (HIP) neurotransmitter efflux.
Results: Bilateral BIC administration into the HIP, but not the PFC, or ip BIC or LUR, to scPCP mice restored NOR ($p<0.05$). However, rescue of NOR, RL and SI was most consistent following GABAA stimulation, particularly GABAA $\alpha 5$ agonism ($p<0.05$), probably acting at tonic extrasynaptic GABAA receptors. The combination of ip LUR and BIC dramatically enhanced GABA efflux in both mPFC and HIP, in scPCP mice only. The effect on LUR to block PCP-induced LMA was prevented by the more potent GABAA antagonist, gabazine ($p<0.05$).
Conclusions: The BIC and gabazine results are consistent with our previous findings of an elevated threshold for LTP in the CA1 of the HIP at excitatory synapses related to increased firing of GABAergic neurons and a postsynaptic strengthening of GABA synapses (Nomura et al 2016). E/I imbalance in the HIP and mPFC differ complicating translating these findings for schizophrenia treatment.
Supported By: Dainippon Sumitomo, Weisman Family Foundation
Keywords: GABA, Hippocampus, Prefrontal Cortex, Phencyclidine, Lurasidone

SYMPOSIUM
Matters of Life: Dissecting Mechanisms of Metabolic Burden in Psychosis, and Moving to Novel Clinical Interventions

3:00 p.m. - 5:00 p.m.
Chair: Vicki Ellingrod
Co-Chair: Anthony Vernon

258. Individualized Long-Term Prediction of the Development of Metabolic Syndrome in Psychotic Disorders: A Machine Learning Approach

Wiepke Cahn[1], Taylor Portner[1], Jessica de Nijs[1], and GROUP Investigators, Hugo Schnack[1]

[1]UMC Utrecht

Background: Metabolic syndrome (MetS) is highly prevalent in psychotic disorders and patients have approximately a two-fold risk of developing MetS as compared to the general population. MetS is a major risk factor for cardiovascular disease and diabetes mellitus type II. The aim of this study is to develop a prediction model for MetS in individual patients with psychosis using machine learning.
Methods: A sample of 588 patients (mean (SD) age = 27.6 (7.4) year) from the Genetic Risk and Outcome of Psychosis (GROUP) study is included in this study. The GROUP study has extensively assessed all patients at baseline, 3- and 6-year follow-up. Subjects were diagnosed with MetS using the International Diabetes Federation (IDF) criteria. A support vector machine is trained to predict MetS at 3-year follow-up based on each of the following sets of baseline data: sociodemographic variables, medical history/somatic complaints, psychiatric illness related variables, medication use and history, substance use characteristics, environmental variables, cognitive task scores, need of care items.
Results: For 3-year MetS the highest, significant, balanced accuracies (BAC) were found for baseline sociodemographic variables (61.4%; $p= < 0.001$) medical history/somatic complaints (64.1%; $p=0.011$), psychiatric illness related (59.6%; $p= <0.001$), cognitive performance (56.2%; $p=0.019$), need of care predictors (57.1%; $p=0.017$).
Conclusions: Our results show that predicting MetS with machine learning can be done with moderate, but significant, accuracies. Our study is an important step in pursuit of personalized medicine applicability in mental health care institutions. However, higher accuracies are necessary for practical use.
Supported By: The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (Zon-Mw, grant number 10-000-1001), and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen Cilag) and universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psychomedical center The Hague. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en De Kempen, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan, Virenze riagg, Zuyderland GGZ, MET ggz, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Zie-

keren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Utrecht: University Medical Center Utrecht and the mental health institutions Altrecht, GGZ Centraal and Delta.)
Keywords: Metabolic Syndrome, Psychotic Disorder, Machine Learning, Prediction

259. Olanzapine Impairs Central Insulin Action: Effects on Body Fuel Preference

Laura Castellani[1], Jennifer Wilkin[1], Zohra Ahsan[1], Chantel Kowalchuk[1], Celine Teo[1], Adria Giacca[2], David Wright[3], Gary Remington[1], and **Margaret Hahn**[1]

[1]Centre for Addiction and Mental Health, [2]University of Toronto, [3]Guelph University

Background: Antipsychotics are widely prescribed but associated with severe metabolic side effects. Olanzapine (OLZ) has been found to impair fat mobilization while shifting major fuel preference from carbohydrates to fats, the later quantified by decreased respiratory exchange ratio (RER). This may involve altered signaling pathways in insulin-sensitive brain areas involved in energy expenditure.
Methods: We investigated the effects of intracerebroventricular (ICV) insulin administration on OLZ-induced disruptions in energy homeostasis. Male Sprague Dawley rats were assigned to 4 treatment groups (ICV-peripheral): Vehicle (VEH)-VEH (n = 5), Insulin (INS)-VEH (n = 7), INS-OLZ (n = 6), VEH-OLZ (n = 5). Rats received injections of INS (10mU) or VEH into the 3rd ventricle, and OLA (3mg/kg) or VEH subcutaneously at the beginning of the light (7AM, t=0) and dark (7PM, t=12h) cycle. Indirect calorimetry was used to calculate RER, and heat production. Cumulative food intake was measured at 12-hour intervals (t=12h and 24 h).
Results: In agreement with previous work OLZ reduced RER ($p=0.016$), independent of changes in heat production or food intake during the dark phase. Unexpectedly, RER also decreased with central insulin administration ($p=0.013$) mirrored by attenuated food intake ($p=0.011$), possibly indicating a shift to fat oxidation characteristic of fasting. An interaction effect ($p=0.007$) was observed between ICV insulin and OLZ treatments on RER, suggesting independent mechanisms influencing fuel preference. Co-administration of OLZ with ICV-INS produced an RER profile similar to OLZ-VEH, suggesting rapid induction of central insulin resistance.
Conclusions: Antipsychotics may perturb central insulin action leading to disruptions in whole body energy homeostasis.
Supported By: Banting Research Foundation
Keywords: Antipsychotics, Intracerebroventricular Insulin, Insulin Resistance, Metabolic Side Effects

260. Effects of Antipsychotic Medications on Adipose Inflammation

Valeria Mondelli[1], Anita Calevro[1], Marie-Caroline Cotel[1], Sridhar Natesan[1], Michel Modo[2], and Anthony C. Vernon[3]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, [2]University of Pittsburgh, [3]King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute

Background: The effect of antipsychotic drug (APD) on either central or peripheral inflammation remains unclear. An important issue in this debate is to what extent the known peripheral metabolic effects of APD, included increased adiposity, contribute to these processes. This study aimed to evaluate the extent to which chronic exposure to haloperidol (HAL) or olanzapine (OLA) resulted in immune activation of rat adipose tissue.
Methods: Visceral adipose tissues were sampled from male Sprague–Dawley rats treated with, haloperidol (2 mg/kg/d s.c., n=8), olanzapine (10 mg/kg/d s.c., n=8) or a common vehicle (n=8), for 8 weeks. From these we obtained a cytokine profile and determined the protein expression levels of F4/80 (a phenotypic macrophage marker) and translocator protein (TSPO) a target for radiotracers thought to indicate microgliosis and commonly used in clinical neuroimaging studies where neuroinflammation is suspected to be involved.
Results: Our data show that OLZ exposure resulted in significantly higher adipose IL-6 levels as compared to vehicle-controls (ANOVA $p=0.013$, Bonferrroni post-hoc test $p<0.05$); in parallel these animals had significantly higher F4/80 expression. There were no significant differences in TSPO protein levels among the three groups. Nevertheless, we found a trend in the correlation between F4/80 and TSPO protein levels in the OLA exposed rats (Pearson $r=0.70$, $p=0.052$).
Conclusions: Taken together, our data suggest that chronic exposure to olanzapine, but not haloperidol, increases immune activation in the adipose tissue, in the absence of a measurable change in TSPO. This may have potentially important consequences in terms of metabolic dysregulation associated with long-term antipsychotic treatment.
Supported By: MRC Grant G1002198
Keywords: Antipsychotics, Inflammation, Metabolic, Adipose Tissue, Olanzapine

261. Metformin and 5-HT2C Agonist Lorcaserin for Weight Loss in Schizophrenia

Lars Jarskog[1] and T. Scott Stroup[2]

[1]University of North Carolina at Chapel Hill, [2]NYSPI/Columbia University

Background: Obesity contributes to cardiovascular disease and shortened lifespans in schizophrenia. Evidence-based treatments for antipsychotic-associated weight gain are limited. Metformin (MET) represents the best-established weight loss intervention in schizophrenia to date. Lorcaserin (LOR), a 5-HT2C agonist approved for weight loss, has not been studied in schizophrenia. While effective, the magnitude of weight loss with either MET or LOR remains modest (~3 kg). Evidence suggests that combination therapy using two agents with different mechanisms-of-action can better overcome endogenous compensatory mechanisms and lead to greater weight loss than either agent alone. Hypothesis: LOR/MET combination treatment is associated with greater weight loss compared to LOR monotherapy or placebo.

Methods: 110 outpatients with schizophrenia or schizoaffective disorder, BMI>27 kg/m2 will be randomized to 52 weeks of LOR monotherapy, LOR/MET combination therapy, or placebo. All participants receive diet and exercise counseling. Primary outcome: differential weight change for LOR/MET combination therapy compared to placebo. Secondary outcomes include differential weight change for LOR monotherapy, measures of glucose and lipid metabolism, appetite-regulating hormones, and change in fat mass, from baseline to end-of-study. Analysis: mixed model approach to repeated measures.
Results: Interim blinded demographic and tolerability data for this NIDDK-funded study will be presented.
Conclusions: This trial will provide evidence-based data for antipsychotic weight management regarding: 1) a novel serotonergic mechanism that promises efficacy and greater psychiatric safety compared to existing sympathomimetic agents, 2) role of augmenting antipsychotic-associated weight loss properties of MET, and 3) extending pharmacological weight intervention treatment duration to 52 weeks, in contrast to shorter-term studies.
Supported By: R01DK105526
Keywords: Weight-Loss Drugs, Antipsychotic, Metformin, Lorcaserin, Weight Gain

SYMPOSIUM
Targeting Hippocampal Dentate Gyrus Neurons in Psychiatric Disorders: Human Molecular Insights

3:00 p.m. - 5:00 p.m.
Chair: Mitsuyuki Matsumoto
Co-Chair: Daniel Weinberger

262. Human Dg-Seq Reveals Cell-Type-Specific Effectors of Schizophrenia Risk

Daniel Hoeppner[1], Andrew Jaffe[2], Joy Ukaigwe[2], Lou Blanpain[2], Ran Tao[2], Ronald McKay[2], Mitsuyuki Matsumoto[3], Joel Kleinman[2], Daniel Weinberger[4], and Thomas Hyde[2]

[1]CNS, Astellas Research Institute of America LLC, [2]Lieber Institute for Brain Development, [3]Astellas Pharma Inc, [4]Lieber Institute for Brain Development, School of Medicine, Johns Hopkins University

Background: The granule cell layer of the Dentate Gyrus (DG-GCL) is an unusually homogeneous cell population. Previous findings linking this important cell type to bipolar disorder and schizophrenia used animal models, induced pluripotent stem cell (iPSC), or low-resolution functional imaging. We therefore sought to isolate and characterize human DG-GCL neurons to better characterize their role in psychiatric disorders.
Methods: We performed laser capture microdissection (LCM) of DG-GCL in postmortem tissue from 263 human subjects diagnosed with schizophrenia (n=75), bipolar disorder (n=66), major depression (n=29), and unaffected controls (n=93), all with genome-wide genotype data. RNA sequencing (RNA-seq) was performed on DG-GCL as well as paired bulk/homogenate hippocampus tissue on a subset of subjects (N=129). Expression quantitative trait loci (eQTL) analysis and differential expression analysis was performed for each diagnosis group.
Results: We identified 5,059 genes differentially expressed between DG-GCLs and homogenate hippocampus ($p < 4.7e-7$). Over 10,000 genes with significant cis-eQTL associations at genome-wide significance (FDR< 1%) were identified, including previously-unannotated transcripts using junction-level analysis (N= 5883). We further identified significant eQTL signal for recently-published genome-wide association study (GWAS) genetic variants for schizophrenia, bipolar, and major depression. Lastly, we identified genes and their features differentially expressed in each psychiatric diagnosis group. Many of these differentially-expressed genes were unique to DG-GCL, showing no corresponding differences in the bulk hippocampus data.
Conclusions: These transcriptional analyses of human DG-GCL demonstrates the potential cell type-specific effects of psychiatric disorders and their genetic risk, and highlight the role of DG-GCL neurons in these disorders.
Supported By: Astellas Research Institute of America; Lieber Institute
Keywords: Dentate Gyrus, RNA sequencing, Human Postmortem Brain, Expression Quantitative Trait Loci (eQTL), Schizophrenia

263. Patterns of RNA-Editing Sites in Hippocampal Dentate Gyrus Neurons

Joo Heon Shin[1], Taeyoung Hwang[2], and Daniel Weinberger[1]

[1]Lieber Institute for Brain Development, [2]University of Colorado Boulder

Background: RNA editing is the co/post-transcriptional modification of single nucleotides in RNA causing a variety of gene products including altered proteins. Although systematic genome-wide profiling of RNA editing sites have been reported from control postmortem human brain across the lifespan, including fetal brain tissue in dorsolateral prefrontal cortex (DLPFC), RNA editing of other brain regions and especially of specific cell populations has not been studied. We will report a unique study of RNA editing in human dentate gyrus neurons and in bulk hippocampal tissue.
Methods: We analyzed the total stranded RNA sequencing data from post-mortem hippocampal dentate gyrus samples (75 schizophrenia, 66 bipolar disorder, 29 major depression and 93 healthy control) isolated by laser capture microdissection and homogenate hippocampus tissues of 452 brain samples (319 healthy control and 133 schizophrenia) for potential novel RNA editing sites.
Results: Our data from hippocampal dentate gyrus and homogenate hippocampus tissue was compared to the previous RNA editing patterns in DLPFC. We previously reported 742 editing sites showing developmentally increasing editing pattern from fetal to adult samples. Compared to these developmentally increasing editing sites, DG and

hippocampus shows different RNA editing patterns. We also have further characterized potential RNA editing sites between controls and psychiatric disorders in DG with varying editing ratios.
Conclusions: We describe patterns of RNA-editing sites in hippocampal dentate gyrus neurons in controls and psychiatric brains compared to the developmentally increasing editing sites. Our data show that cell type specific sampling offers unique insights into illness associated editing patterns.
Keywords: RNA Editing, Dentate Gyrus, RNA-seq

264. Unique Molecular Correlates of Schizophrenia and its Genetic Risk in the Hippocampus Compared to Frontal Cortex

Leonardo Collado Torres[1], Emily Burke[1], Joo Heon Shin[1], Richard Straub[1], Ran Tao[1], BrainSeq Consortium[2], Thomas Hyde[1], Joel Kleinman[1], Daniel Weinberger[1], and **Andrew Jaffe**[1]

[1]Lieber Institute for Brain Development, [2]BrainSeq Consortium

Background: We previously identified widespread genetic, developmental, and schizophrenia-associated changes in polyadenylated RNAs in the dorsolateral prefrontal cortex (DLPFC), but the landscape of hippocampal (HIPPO) transcription using RNA sequencing is less well-explored.
Methods: We performed RNA-seq using RiboZero on 891 RNA-seq samples across 546 individuals (177 with schizophrenia) in DLPFC (N=449) and HIPPO (N=442). We quantified expression of multiple feature summarizations of the Gencode v25 reference transcriptome, including genes, exons, splice junctions and transcripts. Within and across brain regions, we modeled age-related changes in controls using linear splines, integrated genetic data to perform expression quantitative trait loci (eQTL) analyses, and performed differential expression analyses controlled for observed and latent confounders.
Results: We identified widespread developmental regulation within the hippocampus - the majority of expressed genes showed significant changes over developing and aging (15,504 at FDR<0.0001), including many (12,135 at FDR<0.0001) with significant region-specific changes. We identified 224 genes differentially expressed by diagnosis (at FDR < 5%) in hippocampus, which were enriched for ubiquitin protein transferase activity (FDR=0.001) and FoxO signaling (FDR=0.007). Only 12 genes were replicated in the DLPFC, suggesting regional heterogeneity of the molecular correlates of schizophrenia diagnosis. We identified widespread genetic regulation of gene expression in HIPPO, with more eQTLs with stronger effect sizes and more transcript specificity using transcript features (>11,000 genes) versus genes (6340). Hundreds of eQTL associations showed significant regional specificity, including several genetic risk loci for psychiatric illnesses.
Conclusions: We show extensive regional specificity of developmental and genetic regulation, and schizophrenia-associated expression differences between the hippocampus and DLPFC.

Supported By: Lieber Institute for Brain Development
Keywords: Human Postmortem Brain, RNA sequencing, Expression Quantitative Trait Loci (eQTL), Schizophrenia, Brain Development and Aging

265. Electrophysiological Measurements of DG Neurons Derived From Bipolar Disorder and Schizophrenia Patients

Shani Stern[1], Maria Carol Marchetto[1], Renata Santos[1], Meiyan Wang[1], Anne Bang[2], Martin Alda[3], and Fred Gage[1]

[1]Salk Institute for Biological Studies, [2]Conrad Prebys Center for Chemical Genomics, Sanford Burnham Prebys Medical Discovery Institute, [3]Dalhousie University

Background: The study of psychiatric disorders was limited by the paucity of adequate models. These disorders are genetically complex, with many candidate-associated genes. Due to this genetic complexity, animal models that were developed did not recapitulate most of the phenotypes associated with the disorders. The introduction of induced pluripotent stem cells (iPSCs) allowed measurement of cellular phenotypes for psychiatric disorders.
Methods: Immortalized lymphoblasts from a cohort of Bipolar disorder patients were reprogrammed into induced pluripotent stem cells. A half of these patients were responsive to lithium treatment, while the other half were non-responsive to lithium treatment. Similarly, fibroblasts from monozygotic twins discordant to schizophrenia were reprogrammed into iPSCs. Using the lab's differentiation protocols into Dentate Gyrus granule neurons, whole cell patch clamp experiments were conducted on PROX1 expressing neurons.
Results: We show that DG BD neurons are hyperexcitable. Moreover, DG neurons were intrinsically different if they were derived from lithium responsive or non-responsive patients, suggesting that these patients may be afflicted by two different disorders. Training a Naïve Bayes classifier on the electrophysiological features predicts with a low error rate the patient's responsiveness to lithium.

In the SCZ cohort, we found that DG granule neurons of the SCZ-affected twins were hypoexcitable. We also found an intermediate state of the non-affected twins.
Conclusions: Interestingly, despite shared genetic variants between SCZ and BPD, and even shared symptoms in patients between the two disorders, we found that the DG granule neurons of BPD were hyperexcitable, whereas DG granule neurons in SCZ were hypoexcitable.
Supported By: The collection of clinical data and lymphoblasts was supported by the Grant No. 64410 from the Canadian Institutes of Health Research (CIHR) (to MA). This work was also supported by the Paul G Allen Family Foundation, Bob and Mary Jane Engman, The Leona M and Harry B Helmsley Charitable Trust Grant No. 2012-PG-MED002, Annette C Merle-Smith, R01 MH095741 (to FHG), U19MH106434 (to FHG) and by The G Harold and Leila Y Mathers Foundation
Keywords: Schizophrenia, Bipolar Disorder, Induced Pluripotent Stem Cell, Dentate Gyrus

Oral Abstracts

Thursday, May 10, 2018

ORAL SESSION
Mental Illness and Brain Imaging
12:30 p.m. – 2:30 p.m.
Chair: Robert Innis

O1. Classification of Patients With Bipolar Disorder Based on DTI Data: Relationship With Clinical Dimensions

Pauline Favre[1], Edouard Duchesnay[1], and Josselin Houenou[2], ENIGMA Bipolar Disorder Working Group

[1]NeuroSpin, CEA Saclay, [2]APHP, CHU Mondor, INSERM, NeuroSpin, CEA Saclay

Background: There is growing evidence for the potential of machine learning techniques for brain-based diagnosis of psychiatric disorders. However, few studies have been conducted to predict the diagnosis of bipolar disorder (BD) based on structural connectivity. This study aims at using machine learning algorithms to identify biomarkers that can be used to classify BD patients from healthy controls (HC) and investigating whether clinical dimensions of BD affect the accuracy of the classification.
Methods: We gathered Diffusion Weighted images (DWI) from 23 studies leading to a sample size of N = 2767 (1440 BD and 1327 HC). We preprocessed DWI images according to the ENIGMA harmonized analysis methods pipeline. Mean fractional anisotropy (FA) from 62 regions of interest (ROI) as well as the average whole-brain FA were entered in linear support vector machine (SVM) binary classifiers with 5-folds cross-validation to identify individuals as patients or controls.
Results: The classification of the whole sample of BD vs. HC showed significant ($p<0.001$) above-chance accuracy (AUC/sensitivity/specificity = 0.62/0.63/0.61). Classifications based on the patients' sub-populations vs. HC did not improve the classification performance [Off lithium: AUC/sensitivity/specificity = 0.59/0.63/0.55; Early Onset: 0.59/0.59/0.58; High Severity: 0.59/0.61/0.57; with psychotic symptoms: 0.47/0.38/0.56].
Conclusions: These results highlight significant but medium accuracy of the classification of BD vs. HC based on diffusion MRI data. Surprisingly, selection of patients with putatively more severe forms of disease did not lead to better classification performance. Nonetheless, BD is a very heterogeneous disease, with multiple facets that remains to be better identified.
Supported By: Fondation Pour La recherche Médicale (FRM)
Keywords: Diffusion Tensor Imaging (DTI), Bipolar Disorder, Support Vector Machine, ENIGMA

O2. Inter-Subject Variability in Bipolar Disorder Using Multi-Modal Imaging Datasets

Gaelle Doucet[1], Dominik A. Moser[1], Won-Hee Lee[1], Maxwell Luber[1], Alexander Rasgon[1], and Sophia Frangou[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Psychiatric disorders, as defined using clinical information, are thought to include patients with heterogeneous pathophysiology. Neuroimaging offers the most direct window into possible heterogeneity in brain structural and functional abnormalities associated with mental illness. Here we used inter-subject correlation (ISC) scores to measure heterogeneity in functional and structural brain imaging phenotypes in patients with bipolar disorder I (BD) compared to healthy volunteers.
Methods: We computed individual ISC scores derived from measures of subcortical volume, cortical thickness, within- and between- network resting-state functional connectivity (rs-FC), in two independent samples (s1 and s2) of patients with BD (s1=44; s2=78) and healthy individuals (s1=50;s2=41). We examined the effect of diagnosis and of clinical and demographic features.
Results: Patients and healthy individuals did not differ in ISC-scores in either sample despite having adequate power to detect an effect if present. Regardless of diagnosis, younger age and higher proportion of male participants were positively associated with ISC in within-network rs-FC and cortical thickness. Within the patient sample, higher antipsychotic dose was positively correlated with ISC in within-network rs-FC and in cortical thickness while higher levels of manic symptoms were associated with higher ISC in the within-network FC.
Conclusions: We demonstrate that ISC provides a reproducible method to investigate inter-subject variability in neuroimaging measures. Moreover, the diagnosis of BD was not associated with greater inter-subject variability than that observed in non-clinical samples, suggesting that the clinical definition of BD is likely to define relatively homogenous grouping of patients with respect to multimodal neuroimaging phenotypes.
Supported By: R01 MH104284-01A1
Keywords: Bipolar Disorder-I, MRI Brain Imaging, Multimodal Imaging, Inter-Subject Variability

O3. Depression Severity Over 18 Months in Adolescent Girls is Associated With Stress-Linked Cortical Morphometry

Elizabeth Bartlett[1], Greg Perlman[1], Christine DeLorenzo[2], Daniel Klein[1], and Roman Kotov[1]

[1]Stony Brook University, [2]Stony Brook University School of Medicine

Background: Harsh environmental exposures (i.e., trauma) are postulated to impact grey matter development, as well as increase vulnerability to depression. However, it remains unclear whether burden of common stressful life events in a typically-developing adolescent sample has connections to cortical grey matter health or whether such neural markers signal risk for adolescent depression. In this study, we aimed to address these gaps using cortical morphometry data collected from a cohort of 232 15-year-old adolescent females.
Methods: FreeSurfer 5.3.0 was utilized to perform whole-brain surface-based morphometry analyses. Burden of life stress in the previous 9 months was calculated using the Stressful Life Events Schedule (SLES; a semi-structured interview). Severity of depressed mood was assessed with the Dysphoria scale from the Inventory of Depression and Anxiety Symptoms (IDAS-II).
Results: Using whole-brain analyses, adolescents with greater burden of life stress exhibit smaller left precuneus ($p=0.037$) and post-central ($p=0.035$) cortical thickness and left superior frontal ($p=0.006$) and right inferior parietal ($p=0.001$) volume. Furthermore, total morphometric reduction in these regions was associated with dysphoric mood at the time of imaging, at 9-months, and 18-months after imaging ($\beta = -0.057$ to -0.065; $p = 0.013$ to 0.027).
Conclusions: Thus, frontal/parietal cortical health is associated with high burden of life stress in a typically-developing adolescent cohort. These results align with findings from preclinical stress models and imaging studies with trauma-exposed youth. Furthermore, stress-linked cortical grey matter reductions appear to signalprotracted increases in depressed mood. Thus, a heavy burden of life stress in a typically-developing cohort may have underappreciated pathophysiological consequences.
Supported By: R01MH093479
Keywords: Adolescence, Stressful Events, Adolescent Depression, Surface-Based Morphometry, Developmental Trajectories

O4. Right Superior Temporal Gyrus Volume as a Biomarker of History of Suicide Attempt in Youth With Treatment-Resistant Major Depressive Disorder

Quinn McLellan[1], T. Christopher Wilkes[1], Rose Swansburg[1], Natalia Jaworska[2], Lisa Marie Langevin[1], and **Frank MacMaster**[3]

[1]University of Calgary, [2]University of Ottawa, [3]University of Calgary/Strategic Clinical Network for Addictions and Mental Health

Background: Growing evidence suggests an endophenotype for suicidality, including brain morphometric features, could provide an improved platform for suicide risk assessment. Reduced right superior temporal gyrus (rSTG) volumes have been implicated in suicidality across psychiatric disorders.
Methods: We investigated rSTG volume in 45 adolescents: 14 with a history of suicide attempt and treatment-resistant depression (TRD), 14 without a suicide attempt history and TRD, and healthy controls ($n=17$). Participants underwent magnetic resonance imaging (MRI) scans on a 3.0 T scanner. Anatomical imaging acquisition parameters as follows: axial, T1 weighted, repetition time=8204 ms, echo time=3.168 ms, flip angle=10 degrees, 226 slices with 0.8 mm thickness, 300×300 matrix. FreeSurfer was used for cortical thickness analysis.
Results: Groups did not significantly differ in age or biological sex. One-way ANCOVA indicated a significant difference in rSTG volume between TRD youth with a history of suicide attempt, TRD youth without a suicide attempt and healthy controls ($F(2,39)=3.274$, $p=0.048$, $\eta = 0.144$). The post-hoc pairwise comparison revealed that the TRD youth with a history of suicide attempt group had significantly smaller rSTG volumes compared with healthy controls ($p=0.018$), which remained significant following the Benjamini-Hochberg procedure.
Conclusions: This work adds to the evidence of a distinct endophenotype for suicidal behavior and adds to the proposal made by Pan et al. (2015), that reduced rSTG volume may be a marker of suicide attempt history in adolescents.
Supported By: Alberta Children's Hospital Foundation, Canadian Foundation for Innovation, Alberta Health Services
Keywords: Adolescent Depression, Superior Temporal Gyrus, Suicidality, Brain Imaging, Gray Matter Volume

O5. Functional Connectivity Abnormalities in Major Depressive Disorder With and Without Co-Morbid Borderline Personality Disorder and Implications for Treatment With TMS

Marc Dubin[1], Irena Ilieva[1], Ashley Cochran[1], Conor Liston[1], and Faith Gunning[1]

[1]Weill Cornell Medical College

Background: Resting state functional connectivity of frontostriatal and limbic networks defines four subtypes of Major Depressive Disorder (MDD), predicting both symptom profiles and response to Transcranial Magnetic Stimulation (TMS) (Drysdale, Nat Med, 23:28-38). Borderline personality disorder (BPD) is characterized by deficits in partially overlapping networks. Here, we investigate the utility of the four depression subtypes to characterize depression with comorbid BPD.

Methods: 24 currently depressed patients with co-morbid BPD; 84 age-, gender-, and HAMD17-matched depressed patients without BPD and 31 healthy controls received resting state fMRI on a Siemens Prisma 3T scanner. Scans were parcellated into 264 functional nodes using the system of Power (Neuron, 72, 665-678). Subjects were assigned depression subtypes using the previously defined classifier (Drysdale, et al).
Results: Functional connectivity was reduced in Limbic Networks in subjects with MDD, with or without BPD, compared to controls. In contrast, functional connectivity in the Cognitive Control Network was reduced in MDD alone compared to controls and elevated in MDD with Co-Morbid BPD relative to controls. Depression Subtype 1, characterized by anxiety, anergia and middle insomnia, was more prevalent in subjects with MDD with Co-Morbid BPD (46%) compared to in MDD alone (27%).
Conclusions: Our results suggest that depression with co-morbid BPD may be characterized by different network abnormalities than depression without this co-morbidity. Further, as Depression Subtype 1 predicts the highest response rate (80%) to TMS targeting the dorsomedial prefrontal cortex (DMPFC), therapeutic TMS for depression with co-morbid BPD should be investigated prospectively.
Supported By: NARSAD, Pritzker Neuropsychiatric Disorders Research Consortium
Keywords: Depression, Borderline Personality Disorder, Resting State Functional Connectivity, Biomarkers, TMS

O6. Task-Related Stability in the Connectome Fingerprint is Sensitive to Mental Illness

Tobias Kaufmann[1], Dag Alnæs[2], Christine L. Brandt[2], Ole A. Andreassen[2], and Lars T. Westlye[2]

[1]Norwegian Centre for Mental Disorders Research, University of Oslo, [2]Norwegian Centre for Mental Disorder Research

Background: Strong evidence indicates brain aberrations in individuals with mental illness. Whereas group-level analyses have provided important imaging-based clues about brain pathophysiology, the diversity of published findings has revealed a large between-subject heterogeneity, making it difficult to translate group-level findings to the individual. However, recent findings indicating that the brain functional connectome comprises a fingerprint-like pattern have opened doors to the individual-level analysis of brain dysfunction.
Methods: Here, we re-analyzed fMRI data from 90 individuals with schizophrenia, 97 with bipolar disorder and 136 healthy controls. In the same scan session, each individual was scanned during a 0-back and a 2-back version of a blocked n-back task. We defined the individual connectome using a functional whole brain atlas and computed an individualized distance measure based on Spearman rank correlation to assess stability of the connectome between task conditions.
Results: Individuals with schizophrenia and bipolar disorders showed higher distance metrics compared to healthy controls, indicating lower within-subject connectome stability in the patient groups. Further, the distance metric increased with age in all groups and lower distance score was associated with higher task performance, covarying for age, sex and diagnostic differences.
Conclusions: Together, our results suggest lower within-subject connectome stability in response to task demands in individuals with schizophrenia and bipolar disorders compared to healthy controls and encourage the use of approaches for individual fingerprinting for moving the field from group-level to within-subject level analyses in psychiatry.
Supported By: Research Council of Norway (#213837, #223273, #204966/F20, #229129), the South-Eastern Norway Regional Health Authority (#2013-123, #2014-097, #2015-073), KG Jebsen Foundation
Keywords: Connectome Fingerprinting, Schizophrenia, Bipolar Disorders, Functional Brain Connectivity, Task fMRI

O7. Modulating Functional Connectivity to Ameliorate Negative Symptoms in Schizophrenia

Roscoe Brady[1], Irene Gonsalvez[1], Jeremy Schmahmann[2], Matcheri Keshavan[3], Alvaro Pascual-Leone[3], and Mark Halko[1]

[1]Beth Israel Deaconess Medical Center, [2]Massachusetts General Hospital, [3]Beth Israel Deaconess Medical Center, Harvard Medical School

Background: In schizophrenia, 'negative' symptom severity predicts functional outcomes. Using a data-driven analysis of resting-state fMRI (rsfMRI), we sought to discover the brain network basis of negative symptoms. Then in a separate cohort, we modulated this network with multiple sessions of brain stimulation, observing the impact on symptomatology.
Methods: Imaging Study: 44 participants with schizophrenia underwent a rsfMRI scan and clinical characterization. A multivariate distance matrix regression (MDMR) analysis of negative symptom severity was performed, examining voxel-wise connectivity correlated with score on the Scale for the Assessment of Negative Symptoms.

TMS-fMRI study: In 15 participants with schizophrenia, we conducted a double-blind, randomized trial of either transcranial magnetic stimulation (TMS) or sham stimulation to a network node identified in the imaging study (cerebellar vermis). Stimulation was delivered twice a day for 5 days. rsfMRI connectivity and negative symptoms were assessed at baseline and 1 week following the last TMS session. We compared within-subject change in functional connectivity to change in negative symptom severity.
Results: In the imaging study, dysconnectivity between right Dorso-Lateral Prefrontal Cortex (DLPFC) and the cerebellar node of the Default Mode Network (DMN) demonstrated the strongest correlation with symptom severity. In the TMS-fMRI

study, within-subject increase in cerebellar-DLPFC connectivity was strongly correlated with decreasing negative symptom severity (r= -.781, p=.005). Active TMS was significantly more efficacious than sham in reducing negative symptoms (p=.032).
Conclusions: Dysconnectivity in a cerebro-cerebellar circuit correlates with negative symptom severity. Neuromodulation of this circuit demonstrates a causal link between circuit connectivity and symptomatology and a potential therapeutic target.
Supported By: Sidney R. Baer Jr. Foundation, NIH KL2TR000168, NIH K23MH100623, NIH R01MH092440
Keywords: Schizophrenia, Negative Symptoms, rTMS, TMS-fMRI, fMRI Resting State

O8. Regional Cerebellar Volumes and Cerebello-Cerebral Structural Covariance in Adolescents With Early-Onset Psychosis: A Multisample Study

Cecilie Johannessen[1], Tiril P. Gurholt[2], Stener Nerland[2], Torgeir Moberget[3], Vera Lonning[2], Runar E. Smelror[4], Kirsten Wedervang-Resell[5], Anne M. Myhre[5], Mathias Lundberg[6], Sophia Frangou[7], Matthew J. Kempton[8], Marinos Kyriakopoulos[9], Bjørn R. Rund[10], Ole A. Andreassen[1], Christian K. Tamnes[10], and Ingrid Agartz[3]

[1]Norwegian Centre for Mental Disorders Research (NORMENT), K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, [2]University of Oslo, Institute of Clinical Medicine, [3]Norwegian Centre for Mental Disorders Research (NORMENT), K.G. Jebsen Centre for Psychosis Research, Oslo University Hospital,, [4]Diakonhjemmet Hospital, [5]Oslo University Hospital, [6]Karolinska Institutet, [7]Icahn School of Medicine at Mount Sinai, [8]Institute of Psychiatry, Psychology & Neuroscience, King's College London, [9]King's College London, [10]University of Oslo

Background: The cerebellum has been proposed to play a central role in schizophrenia. In line with this hypothesis, recent results from a study of adults with schizophrenia spectrum disorders showed cerebellar volume reductions with effect sizes similar to the most consistently reported cerebral effects. However, cerebellar involvement in early-onset psychosis (EOP) is not well characterized and may inform us on the ontogeny of the disorder.
Methods: We investigated cerebellar volumes and cerebello-cerebral structural covariance using magnetic resonance imaging (MRI) data from 106 adolescents with EOP and 122 healthy controls (HCs) aged 12-18 years from five European samples, using analysis pipelines optimized for both the cerebellum and the cerebrum. Cerebellar grey matter volumes were estimated in seven functionally defined regions of interest (ROIs) based on an fMRI connectivity study. Our primary analyses tested for case-control differences while controlling for sample, age and sex, while follow-up analyses explored associations with demographic, clinical and cognitive data.
Results: Our results showed that regional cerebellar volumes were reduced in EOP relative to HCs. Specifically, we observed lower volumes in the cerebellar ROIs with functional connectivity with the cerebral dorsal attention ($p = .003$, $eta2 = .040$) and ventral attention ($p = .017$, $eta2 = .026$) networks. Similar results were found when additionally controlling for intracranial volume. There were no interactions between group and age or sex.
Conclusions: The present study showed reduced regional cerebellar volumes in adolescents with EOP and suggest that the cerebellum may have an important role in the early pathophysiology of psychosis.
Supported By: Forskningsrådet
Keywords: Cerebellum, Structural Covariance, MRI, Early-Onset Psychosis, Adolescents

ORAL SESSION
Neuroendocrinology, Anxiety & Treatment Strategies
3:00 p.m. – 5:00 p.m.
Chair: Luan Phan

O9. Childhood Abuse Increases Risk for Anxious Depression by Altering GR-Sensitivity

Andreas Menke[1], Dominik Lehrieder[1], Catherina Wurst[1], Saskia Stonawski[1], Jasmin Fietz[1], Karin Lechner[1], Amelie Sauter[1], Carolin Leistner[1], Yasmin Busch[1], Juergen Deckert[1], and Katharina Domschke[2]

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Background: Anxious depression is a common subtype of major depressive disorder (MDD) and is associated with greater severity and poorer outcome. Alterations of the hypothalamic-pituitary-adrenal (HPA) axis, especially of the glucocorticoid receptor (GR) function are often observed in MDD and childhood adversity influences both the risk of MDD and the function of the HPA axis, therefore we investigated GR function in anxious depression in dependency of childhood adversity.
Methods: We enrolled 103 depressed in-patients. Anxious depression was defined using the Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor score $\geq$7. Blood draws were performed at 6pm before and 3 hours after 1.5 mg dexamethasone (dex) ingestion for measurement of cortisol, ACTH and blood count to assess the function of the HPA axis. Childhood adversity was evaluated using the Childhood Trauma Questionnaire.
Results: We identified 55 patients (53.4%) with anxious depression who showed a greater severity and worse outcome. These patients were more often exposed to sexual abuse (30% vs 16%, p=0.09) and neglect (57%

vs. 34%, p=0.02) than patients with non-anxious depression. Dex led to a significant suppression of cortisol after 3h in all participants. However, only in patients exposed to childhood abuse there was a significant triple interaction between dex, anxious depression and childhood abuse (F=8.694; p=0.004) with a reduced cortisol suppression in anxious depression. Additionally, the dex-induced increase in leucocytes was blunted only in patients with anxious depression exposed to trauma (F=4.212; p=0.04).
Conclusions: These results indicate that childhood abuse predisposes to an anxious subtype of MDD via an impairment of GR function.
Supported By: IZKF, BMBF
Keywords: HPA Axis, Anxious Depression, Dexamethasone, Depression, Childhood Trauma

O10. Neuronal Chromatin Dynamics and Anxiety-Related Phenotypes Across the Estrous Cycle

Ivana Jaric[1], Devin Rocks[1], John M. Greally[2], Masako Suzuki[2], and **Marija Kundakovic**[1]

[1]Fordham University, [2]Center for Epigenomics, Albert Einstein College of Medicine

Background: Anxiety and depression are two times more prevalent in women than men. Sex-hormone fluctuation is likely a major risk factor for female's increased vulnerability, although mechanism(s) are unknown. Epigenetic mechanisms are implicated in anxiety and sex hormones regulate chromatin organization, but this remains underexplored in the brain. An understanding of how fluctuating estrogen levels affect chromatin and gene expression in the brain will provide critical insights into the mechanisms underlying sex- and hormone-dependent variations in anxiety-related phenotypes.
Methods: After estrous-cycle determination, 20 adult female mice in diestrus (low-estrogen phase), 20 females in proestrus (high-estrogen), and 20 males underwent anxiety tests (open-field, light-dark-box, elevated-plus-maze). ATAC-seq on FACS-purified neuronal nuclei was used to assess neuronal chromatin organization in the ventral hippocampus, an anxiety-relevant area. We further examined candidate gene expression (qRT-PCR) and protein localization (confocal microscopy).
Results: Female mice in diestrus exhibited increased anxiety-like behavior compared to proestrus females and males, implying that a physiological drop in estrogen increases anxiety risk. We detected differential chromatin accessibility in: >20,000 genomic regions in diestrus vs. proestrus females; >19,000 regions in diestrus females vs. males; >20,000 regions in proestrus females vs. males. Estrous-cycle- and sex-related chromatin (re)organization was detected in regulatory regions and associated with differential gene expression, including genes important for synaptic function, neurotransmission, and behavior.
Conclusions: These data provide candidate genes and pathways contributing to within- and between-sex differences in anxiety-related behavior. Unraveling the mechanisms through which sex hormones dynamically affect brain function and behavior will facilitate the development of sex-specific treatments for anxiety and depression.
Supported By: NARSAD Young Investigator Award
Keywords: Epigenetics, Anxiety, Sex Hormones, Sex Differences, Chromatin

O11. Impact of Adverse Childhood Experiences on Behavioral and Neural Markers of Executive Function in Menopausal Women

Sheila Shanmugan[1], James Loughead[1], Mary D. Sammel[1], Theodore Satterthwaite[2], Wen Cao[1], Erica Baller[1], Kosha Ruparel[1], Ruben Gur[1], and C. Neill Epperson[3]

[1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania, [3]Perelman School of Medicine at University of Pennsylvania

Background: Many healthy women with no history of cognitive dysfunction experience subjective executive difficulties during menopause. We hypothesized that adverse childhood experiences (ACE) increase the risk of executive dysfunction during menopause via alterations in monoaminergic neurotransmission.
Methods: We evaluated the effect of ACE on subjective and objective measures of executive function as well as executive activation, functional connectivity, and neurochemistry. We used tryptophan depletion (TD) to probe serotonergic function both pre and post estradiol administration and used lisdexamfetamine (LDX) to probe catecholaminergic function.
Results: ACE moderated the impact of TD on DLPFC activation ($p = 0.0001$) and within-network connectivity ($p = 0.1$) in hypogonadal women. Treatment with estradiol attenuated the effects of both ACE and TD on DLPFC activation (4-way interaction $p = 0.03$). ACE also moderated the impact of LDX on insular activation (p=0.06) and symptoms of executive dysfunction (p=0.01). While LDX increased activation in the insula (p=0.01) and reduced symptoms related to difficulty with organization and activation for work (p=0.0002) in the high ACE group, insular activation and symptom severity with LDX was not significantly different from placebo in the low ACE group.
Conclusions: Results suggest that early life adversity has latent impacts on serotonergic circuits underlying executive function that are unmasked by loss of estradiol during menopause. Additionally, they indicate that early adversity may have lasting effects on catecholaminergic neurotransmission and may moderate response to stimulant medications. Together, they emphasize the importance of considering ACE when treating executive difficulties with pharmacologic agents during menopause.
Supported By: P50 MH099910 (Epperson), Penn PROMOTES Research on Sex and Gender in Health (Epperson), Shire Pharmaceuticals, R01MH107703 (Satterthwaite), F30AG055256 (Shanmugan)

Keywords: Executive Function, Adverse Childhood Experiences, Estradiol, Acute Tryptophan Depletion, Lisdexamfetamine

O12. Intranasal Testosterone Reduces Stress-Evoked Anxiety in Women

Ellie Shuo Jin[1] and Robert Alan Josephs[1]

[1]The University of Texas at Austin

Background: Can a single-dose of a testosterone-containing nasal spray reduce anxiety? Although both exogenous and endogenous testosterone have been associated with reductions in implicitly measured fear responses, it remains unknown whether exogenous testosterone can reduce the explicit, subjective experience of anxiety in humans.
Methods: In the present study, participants (N = 104, 48.1% female) were randomly assigned to receive either testosterone or placebo via intranasal spray before taking part in an acute psychosocial stressor. Participants used visual analogue scales to rate their subjective anxiety before, during, and after the stressor.
Results: Results revealed a statistically significant drug by sex interaction, in which women—as expected—experienced significantly higher levels of subjective anxiety in the placebo condition compared to men; a sex difference that was eliminated in the drug condition. Further, women randomized to the testosterone condition experienced significantly lower levels of anxiety during recovery from the acute stressor relatively to women in the placebo condition.
Conclusions: Taken together, these results have important implications for the etiology of anxiety and treatment.
Keywords: Anxiety, Testosterone, Neuroendocrinology, Sex-steroid Hormones, Gender Differences

O13. Delayed Treatment and Co-Occurring Psychiatric Illness Predict Response to Gamma Knife Capsulotomy for Obsessive Compulsive Disorder

Adriel Barrios-Anderson[1], Nicole McLaughlin[1], Richard Marsland[2], Georg Noren[1], Wael Asaad[1], Benjamin Greenberg[3], and Steven Rasmussen[3]

[1]Butler Hospital, Alpert Medical School of Brown University, [2]Psychiatric Neurosurgery Program, Butler Hospital, [3]Butler Hospital, Alpert Medical School of Brown University, Psychiatric Neurosurgery Program, Center for Neurorestoration and Neurotechnology, Providence VA Medical Center

Background: Ten percent of patients with OCD exhibit severe symptoms that do not improve with standard behavioral and pharmaceutical therapy. Gamma Ventral Capsulotomy (GVC) has a proven efficacy of 55-80% in treating patients with medically-refractory OCD, but it is unknown what factors distinguish responders from non-responders.
Methods: We conducted retrospective chart-analysis on a dataset of OCD patients treated with GVC (N=66) from 1993 to 2016. We examined the age of OCD symptom onset and age at initial OCD treatment to calculate the time to treatment in years. We also looked at the co-incidence of Axis I psychiatric illnesses. Patient outcome 6 months post-surgery was assessed with the Yale-Brown Obsessive Compulsive Scale (YBOCS).
Results: On average, OCD symptoms began at age 11, and standard OCD treatment began at age 20. Greater time to treatment correlated with more severe post-surgical YBOCS ($p=0.04$) and reduced response compared to baseline ($p= 0.03$). Co-occurring psychiatric illness was a common finding in this sample (87.9%). We found that the greater the number of co-occurring diagnoses, the higher the post-surgical YBOCS ($p=0.03$) but not pre-surgical YBOCS ($p=0.92$).
Conclusions: This study examined predictors of outcome in one of the largest samples of patients who have undergone GVC for severe OCD. Our data suggest that surgical outcome is associated with time to OCD treatment, as well as the number of co-occurring psychiatric illnesses. Earlier treatment may make OCD symptoms more amenable to surgical treatment. Conversely, co-occurring diagnoses may limit post-surgical response by increasing disease burden and potentially affecting underlying functional neurocircuitry.
Supported By: 5K23MH100607
Keywords: Psychiatric Neurosurgery, Obsessive Compulsive Disorder (OCD), Prediction of Treatment Outcome

O14. Deep TMS of the Medial Prefrontal and Anterior Cingulate Cortices for OCD: A Double-Blinded Multi-Center Study

Aron Tendler[1], Joseph Zohar[2], Lior Carmi[2], Yiftach Roth[1], and Abraham Zangen[3]

[1]Brainsway Ltd., [2]Tel Aviv University, [3]Ben Gurion University

Background: Obsessive compulsive disorder (OCD) is a common disabling disease, yet medications only result in a reduction of symptoms for 40-60% of patients. Symptom severity is correlated to the degree of hyperconnectivity in the cortical-striatal-thalamic-cortical circuit and increased glucose metabolism in the anterior cingulate cortex during symptom provocation and at rest.
Methods: Ninety-four OCD patients were randomized to receive twenty-nine active or sham treatments over six weeks. Deep transcranial magnetic stimulation(dTMS) was applied over the medial prefrontal(mPFC) and anterior cingulate cortices(ACC) using the H7 dTMS coil. Immediately after individualized symptom provocation dTMS was administered at 100% resting motor threshold of the foot, 20HZ

pulse frequency, in 2 second trains, with a 20 second inter-train interval totaling 2000 pulses. The sham coil was designed to have the same sound and feel as the real coil without stimulating the brain.
Results: At the end of week 6 the YBOCS decreased by 5.7 points in the dTMS arm and by 3.0 points in the sham arm (p-value: 0.0157). Response rates were (≥30% YBOCS reduction) 38.10% in the dTMS arm and 11.11% in the sham arm (p-value:0.0033). Partial response rates were (≥20% YBOCS reduction) 54.76% in the dTMS arm and 26.67% in the sham arm (p-value: 0.0076). At week 10 the YBOCS decreased by 6.2 points in the dTMS arm and by 3.8 points in the sham arm (p-value: 0.0459).
Conclusions: High frequency dTMS of the mPFC/ACC with the H7 coil is an effective treatment for OCD.
Supported By: Brainsway Ltd.
Keywords: Deep TMS, rTMS, HF-rTMS, Obsessive Compulsive Disorder (OCD)

O15. Unsupervised Machine Learning to Classify Euthymic Bipolar Individuals Into Putative Subtypes

Stephanie Njau[1], Jenniffer Townsend[2], Gerhard Hellemann[3], Benjamin Wade[4], Susan Bookheimer[1], Katherine Narr[4], and John Brooks[1]

[1]University of California, Los Angeles, UCLA School of Medicine, [2]University of California, San Francisco, [3]UCLA Semel Institute for Neuroscience and Human Behavior, [4]University of California, Los Angeles

Background: Differences in functional brain activation are reported in bipolar disorder relative to controls. Yet, differential treatment response suggests that bipolar disorder is not homogeneous. In this study we sought to define subtypes of bipolar disorder as defined by neural activation of networks underlying emotion regulation.
Methods: We computed regional functional activation measures in 84 euthymic bipolar disorder 1 subjects (39.14 +/- 12.48 yrs; 36F) during an emotional regulation task requiring down-regulation of negative appraisal of visual stimuli. Mean time-course values were extracted from 25 regions focusing on fronto-striatal and limbic areas previously shown to activate differentially in bipolar disorder and utilized as features into agglomerative hierarchical clustering. We used the Hamilton Depression Rating Scale (HAM-D) and Emotion Regulation Questionnaire (ERQ) to measure differential phenotypic expression of the neural subtypes.
Results: Analyses revealed three distinct clusters of subjects primarily defined by 1) hyperactivation of subgenual cingulate (sgACC) and relative hypoactivation of limbic and dorsolateral prefrontal regions, 2) relative hyperactivation of dorsolateral and medial prefrontal regions, and hypoactivation of ACC, and 3) hyperactivation in limbic regions and hypoactivation in sgACC. A profile analysis in a patient sub-sample revealed differential profiles with respect to sub-syndromal depressive symptoms ($p = .03$). A trend was also observed with respect to mean self-report measures of ERQ re-appraisal ($p = .09$) and suppression ($p = .09$).
Conclusions: Our findings provide the first evidence of neural subtypes within BD and suggest the potential for establishing objective 'bottom-up' approaches for classifying patients which may provide pathways for personalized treatment regimens.
Supported By: RO3
Keywords: Bipolar Disorder, Machine Learning, Subtypes, BOLD Functional MRI, Emotional Regulation

O16. The Impact of Medical Residency Training on Cellular Aging

Kathryn Ridout[1], Samuel Ridout[2], Constance Guille[3], Douglas Mata[4], and Srijan Sen[5]

[1]Kaiser Permanente, [2]Brown University, [3]Medical University of South Carolina, [4]Harvard Medical School, [5]University of Michigan

Background: Internship, the first year of graduate medical education, is a stressful period. While evidence suggests that residency-related stress negatively impacts well-being, studies of objective biological markers quantifying the impact of stress on resident health are lacking. Telomeres are a biological marker of stress exposure and predict disease risk. This study aimed to examine associations between internship stress and telomere length.
Methods: Physicians in training provided DNA for telomere analysis prior to and after intern year. Psychological and demographic factors were measured at baseline and residency and non-residency related stressors measured quarterly during internship.
Results: 250 interns participated in this study. The mean age was 27.42.9 years; 47.6% were male. Telomeres shortened by 143.5839.1 base pairs across intern year, equivalent to 6 years of typical cellular aging. Telomere length was associated with sex, neuroticism and early life stress at baseline; age was associated with change in telomere length ($P<0.05$). Higher duty hours were associated with greater changes in telomere length ($P=0.03$) with −2561001 base pairs of telomere attrition for interns working 80 hours or more per week compared to −42648 base pairs for interns consistently working less than 80 hours a week ($t(147)=2.01$, $P=0.046$).
Conclusions: Residents experienced accelerated telomere attrition over internship year. In addition to established risk factors, duty hours predicted telomere attrition. This work identifies objective, biological sequelae of residency stress and highlights the need for reforms. Telomere length may potentially serve as a tool to monitor the effectiveness of interventions aimed at improving the residency training environment.
Supported By: R01 MH101459 and The Pritzker Foundation
Keywords: Telomere, Residency, Training, Aging, Stress

Friday, May 11, 2018

ORAL SESSION
Networks and Connectivity
12:30 p.m. – 2:30 p.m.
Chair: Jeff Daskalakis

O17. Connectomics in Subcallosal Cingulate Deep Brain Stimulation: Effective Connectivity as a Biomarker for Target Engagement

Patricio Riva Posse[1], Allison Waters[1], Kisueng Choi[1], and Helen Mayberg[2]

[1]Emory University, [2]Emory University School of Medicine

Background: Responders to deep brain stimulation (DBS) in the subcallosal cingulate (SCC) share stimulation on a stereotypic connectome of converging white matter bundles. A tractography-based target selection using a "connectome blueprint" of past DBS responders shows improved results. While this structural pattern is a necessary requirement for antidepressant efficacy, there has been no functional evidence describing the distinction between effective and non-effective contacts.
Methods: Four subjects were implanted with DBS in the SCC using a tractography-based approach. Stimulation from effective and non-effective contacts was performed (2 Hz, 6 V), and the cortical evoked response (ER) was captured with 256-channel EEG.
Results: Magnitude of the ER to unilateral left stimulation is greater following stimulation from effective versus non-effective contacts, with a different signal emerging in dorsolateral prefrontal cortex (DLPFC). Source analysis shows greater ER magnitude from the effective target in left DLPFC between 60ms and 100 ms from the initiation of the propagation pattern. Coincident scalp topography appears as a positive focus over dorsal anterior midline that migrates in the posterior direction and is reliable across individuals.
Conclusions: Absence of objective biomarkers to guide target selection and stimulation parameter setting is a barrier to adequate implementation of SCC DBS. A non-invasive metric of effective connectivity from a white matter target in the subcallosal cingulate has the requisite properties of a biomarker of the effective contacts. This putative biomarker showing involvement of DLPFC in effective stimulation may be informative and relevant to the mechanism of treatment efficacy.
Supported By: Hope for Depression Research Foundation
Keywords: Subcallosal Cingulate, Deep Brain Stimulation, DLPFC, EEG, Treatment Resistant Depression

O18. Changes in Effective Hippocampal Network Coupling Mediate Learning and Memory of Associations Between Temporally Discontiguous Stimuli

Mohsin Ahmed[1], James Priestley[2], Angel Castro[2], Fabio Stefanini[3], Elizabeth Balough[2], Erin Lavoie[4], Luca Mazzucato[3], Stefano Fusi[3], and Attila Losonczy[2]

[1]College of Physicians and Surgeons, Columbia University/New York State Psychiatric Institute, [2]Columbia University, [3]Center for Theoretical Neuroscience, Columbia University, [4]New York State Psychiatric Institute

Background: Episodic memory requires linking discontiguous events in time and depends on the hippocampus. This temporal association learning is often modeled using trace fear conditioning. Here we probe the ensemble activity in hippocampal CA1 during trace fear learning to differentiate between candidate activity mechanisms and directly resolve the underlying representation.
Methods: We integrated optogenetics and two-photon calcium imaging with a differential auditory 'trace' fear conditioning (15s 'trace') paradigm in head-fixed, water-deprived mice. We used suppression of licking behavior for water as a measure of conditioned fear. We analyzed CA1 network activity dynamics using linear classifiers (SVM with linear kernel) to decode relevant variables and assess the information encoded by the population with learning.
Results: We find that learning is dependent on dorsal CA1 activity ($n=5$/group; $p<0.05$, t-test) and mice ($n=7$) reliably discriminate between fearful and neutral conditioned stimuli (CS). Imaging of CA1 network dynamics ($n=1200$ neurons/4 mice) show that neither previously proposed mechanisms of temporal sequence nor 'persistent' activity are congruent with the observed population code. Instead, CS identity can be reliably decoded from the covariance of neural activities, which defines the effective network couplings, during both CS and 'trace' intervals.
Conclusions: Our studies suggest that CS identity is encoded by combinatorial patterns of cell activation, which develop with learning but occur at different times across trials. Thus, we propose a new model of trace fear learning where certain CA1 coactivity patterns are transiently potentiated and can be used to query information about the cue identity throughout the trial, without requiring an uninterrupted representation.
Supported By: NIMH K08, T32, and R01; Leon Levy Foundation
Keywords: Hippocampus, Associative Learning, Systems Neuroscience, Two-Photon Imaging, Fear Memory

O19. Electroconvulsive Therapy Modulates Gray Matter Increase in a Hub of an Affect Processing Network

Julia Camilleri[1], Felix Hoffstaedter[1], Maxim Zavorotny[2], Robert Christian Wolf[3], Philipp A. Thomann[3], Ronny Redlich[4], Udo Dannlowski[4], Michael Groezinger[5], Traute Demirakca[6], Alexander Sartorius[6], Simon Eickhoff[7], and **Thomas Nickl-Jockschat**[8]

[1]Juelich Research Center, [2]University of Marburg, [3]University of Heidelberg, [4]University of Muenster, [5]Psychotherapy and Psychosomatics, RWTH Aachen University, [6]Central Institute for Mental Health, [7]Heinrich-Heine University Duesseldorf Institute for Clinical Neuroscience, [8]University of Iowa Carver College of Medicine

Background: A growing number of recent studies have suggested that the neuroplastic effects of electroconvulsive therapy (ECT) might be prominent enough to be detected through changes of regional gray matter volume (GMV) during the course of the treatment. Since ECT patients are difficult to recruit for imaging studies, most publications, however, report only on small samples. Addressing this challenge, we here report results of a structural imaging study on ECT patients that pooled patients from multiple German sites.
Methods: A whole-brain voxel-based morphometry (VBM) analysis was performed in order to detect structural differences in 85 patients with unipolar depression before and after ECT, when compared to 86 healthy controls. Both task-independent and task-dependent physiological whole-brain functional connectivity patterns of these regions were modeled. All emerging regions were additionally functionally characterized using the BrainMap database.
Results: Our VBM analysis detected a significant increase of GMV in the right hippocampus/amygdala region in patients after ECT compared to healthy controls (Figure 1a). This region was enrolled in a network associated with emotional processing and memory. A region in the left fusiform gyrus with higher GMV in controls when compared with patients at baseline showed only minor changes after ECT (Figure 1 b,c).
Conclusions: Our data points to a GMV increase in patients post ECT in regions that seem to constitute a hub of an emotion processing network. This appears as a plausible antidepressant mechanism and could explain the efficacy of ECT not only in the treatment of unipolar depression, but also of affective symptoms across heterogeneous disorders.
Supported By: JARA-Brain Seed Fund
Keywords: Electroconvulsive Therapy (ECT), Major Depression, Brain Imaging

O20. Increased Functional Connectivity Between Ventral Attention and Default Mode Networks in Adolescents With Bulimia Nervosa

Mirjana Domakonda[1], Xiaofu He[1], Seonjoo Lee[2], Marilyn Cyr[1], and Rachel Marsh[1]

[1]Columbia University & New York State Psychiatric Institute, [2]Columbia University Medical Center

Background: Bulimia nervosa (BN) is characterized by excessive attention to self and, specifically, body shape and weight, but the ventral attention (VAN) and default mode (DMN) networks that support attentional and self-referential processes are understudied. We sought to assess whether altered functional connectivity within and between these networks contributes to such excessive concerns early the course of BN.
Methods: Resting-state functional magnetic resonance imaging scans were acquired from 33 BN and 37 healthy comparison (HC) adolescents (aged 12 to 21 years) group-matched by age and body mass index. Region-of-interest analyses were performed to examine group differences in functional connectivity within and between the VAN and DMN. We further explored associations of VAN-DMN connectivity with BN symptoms, body shape and weight concerns, and sustained attention on the Continuous Performance Test (CPT).
Results: Compared to HC adolescents, those with BN showed significantly increased connectivity between right ventral supramarginal gyrus and all DMN regions, as well as between right ventrolateral prefrontal cortex and left lateral parietal cortex. Within-network connectivity did not differ between groups. VAN-DMN connectivity was associated with BN severity and body shape/weight concerns in the BN group. No significant group-by-CPT interactions on VAN-DMN connectivity were detected.
Conclusions: Increased VAN-DMN connectivity in adolescents with BN may reflect abnormal engagement of VAN-mediated attentional processes at rest, likely due to their preferential attention to self-referential thoughts about shape and weight. Future studies should further investigate these circuits as targets for the development of early interventions aimed at decreasing excessive body shape/weight concerns.
Supported By: K01-MH077652; R01MH0900062
Keywords: Adolescence, Bulimia Nervosa, Resting State fMRI

O21. Neural Correlates of Fear Learning in a Large, Clinically Diverse Community Sample

Namik Kirlic[1], Robin Aupperle[1], Rayus Kuplicki[1], and Martin Paulus[1], Tulsa 100 Investigators[1]

[1]Laureate Institute for Brain Research

Background: The dysregulation of fear learning has been linked to a number of psychiatric disorders. While amygdala-insula-prefrontal (PFC) circuitry is considered important for fear learning, there have been inconsistencies in the human literature. We sought to clarify neural response patterns during fear learning in a large, clinically diverse community sample.
Methods: As part of Tulsa 1000, an ongoing, naturalistic longitudinal study based on NIMH RDoC framework, 415 adults (45 healthy subjects; 370 with affective, eating, and substance use disorders) completed a fear learning task consisting of familiarization, acquisition (early, late), and extinction (early, late). During acquisition, one of the conditioned stimuli was paired with a loud scream (CS+), while the other was not (CS-). During extinction, CS+ were presented without aversive stimuli. Linear mixed-effects analyses examined time by condition effects on activation (CS+ versus CS-) extracted from spheres within insula, amygdala, and ventromedial PFC.
Results: Results revealed a main effect of time and condition for left [$F(3,2898)=5.14$, $p<.01$; $F(1,2898)=4.15$, $p<.05$] and right insula [$F(3,2898)=4.97$, $p<.01$; $F(1,2898)=8.69$, $p<.01$], characterized by greater activation to CS+ versus CS- and decreased activation over time. Insula activity related to task anxiety across all phases and skin conductance responses ($n=175$) during early acquisition and extinction ($p<.05$). There were no effects on amygdala or vmPFC activation.

Conclusions: These preliminary results, focused on predefined regions, failed to replicate amygdala-vmPFC changes during fear learning. Findings confirmed the insula's role in fear learning and experiences of subjective anxiety. Future investigations using computational methods could be useful in clarifying neural mechanisms of fear learning.
Supported By: William K. Warren Foundation
Keywords: Fear Conditioning and Extinction, Insula, Amygdala, Ventromedial PFC

O22. Transcranial Magnetic Stimulation Reveals Symptom-Related Brain Network Abnormalities in Depression

Colleen Mills-Finnerty[1], Carena Kole[1], Rachael Wright[1], and Amit Etkin[1]

[1]Stanford University

Background: Causal understanding of the brain abnormalities that give rise to depression is urgently needed so that targeted, neurobiologically informed interventions can be developed. Transcranial Magnetic Stimulation (TMS) to the dorsolateral prefrontal cortex (DLPFC) is increasingly being used as a treatment for depression, however most interventions are "one size fits all" as the mechanism by which DLPFC TMS remediates brain circuits remains unknown. The present study thus used TMS as a causal probe of brain network integrity in untreated depression patients compared to healthy controls, to identify deficits specific to patients that may be remediated by rTMS treatment.
Methods: Using single pulse TMS to right and left DLPFC concurrent with neuroimaging (TMS/fMRI), we compared TMS response in healthy controls (n=30) to that of unmedicated patients with MDD (n=38). Analyses were performed using FMRIB Software Library and R.
Results: Whole brain Generalized Linear Model (GLM) analyses identified significant group differences in right DLPFC TMS-induced response in the medial prefrontal cortex (mPFC; corrected for multiple comparisons). GLM analysis also identified TMS-induced mPFC response that was significantly predicted by depressive symptoms (MASQ-D, $p<.005$).
Conclusions: These results replicate previous findings that DLFPC exerts causal control to decrease mPFC activation in healthy people, and demonstrates for the first time that this relationship breaks down in depression. These results point to remediation of this causal relationship as a potential mechanism of TMS efficacy in reducing symptoms of depression.
Supported By: NIMH RO1
Keywords: Depression, Transcranial Magnetic Stimulation, BOLD fMRI, Medial Prefrontal Cortex, Dorsolateral Prefrontal Cortex

O23. Dysfunction of Brain Networks in Obsessive-Compulsive Disorder is Related to the Severity of Symptoms

Christiaan Vriend[1], Bastiaan Bijleveld[1], Linda Douw[1], Stella J. de Wit[1], Ysbrand D. van der Werf[1], and Odile A. van den Heuvel[2]

[1]VU Medical Center, [2]Haukeland University Hospital; VU Medical Center

Background: Obsessive-compulsive disorder (OCD) is a debilitating neuropsychiatric disorder, characterized by obsessions and compulsions. The pathophysiology of OCD is still incompletely understood although cortico-striatal-thalamo-cortical circuit dysfunction has been implicated. Graph-based network analyses are increasingly employed to study the pathophysiology of brain disorders, but few studies have used this methodology in OCD.
Methods: Using graph analyses and resting-state fMRI, we investigated network topology in 45 medication-free OCD patients, 19 unaffected siblings and 41 well matched healthy controls. We examined whole-brain differences in network topology using the Brainnetome atlas, focusing on efficiency and clustering coefficient; graph indices that measure the ability to integrate and segregate information within the network, respectively. We used permutation tests for statistical analyses (5000 permutations).
Results: Using a three-group comparison we observed no significant differences. However, when splitting the OCD group based on clinical severity (Yale-Brown obsessive-compulsive scale$\geq$23), patients with severe OCD (n=19) exhibited markedly reduced efficiency and clustering at the global level compared with mild OCD (n=26; efficiency: P=.02, clustering: P=.03) and siblings (efficiency: P=.03, clustering: P=.02). Patients with mild OCD did not differ from healthy controls or siblings.
Conclusions: Our results show that severe but not mild OCD is associated with a decreased ability to integrate and segregate information within brain networks. These findings indicate that symptom severity is a relevant factor to consider in network analyses and suggests that severe OCD is associated with global network dysfunction whereas mild OCD may be related to more localized dysfunction.
Supported By: Netherlands Organisation for Scientific Research (NWO-ZonMw VENI grant 916.86.036, dr. O.A. van den Heuvel), Brain & Behavior Research Foundation (NARSAD Young Investigators Award 2009, dr. O.A. van den Heuvel), the Netherlands Brain Foundation (2010(1)-50), and the Amsterdam Brain Imaging Platform.
Keywords: Graph Analysis, Obsessive Compulsive Disorder (OCD), Resting State fMRI, Symptom Severity, Medication-Free

O24. Altered DLPFC-Precuneus Connectivity in PTSD: Morphological, Clinical, and Fear Conditioning Correlates

Elizabeth Olson[1], Roselinde Kaiser[2], Scott Rauch[1], and Isabelle Rosso[1]

[1]McLean Hospital/Harvard Medical School, [2]University of California, Los Angeles

Background: The dorsolateral prefrontal cortex (DLPFC) plays a critical role in working memory and regulatory aspects of

cognitive control. Altered DLPFC structure and function have been demonstrated in trauma-exposed samples, and changes in DLPFC resting state functional connectivity (rsFC) have been empirically identified in prior studies focused on other network hubs. We aimed to specifically identify clinical and behavioral deficits associated with altered DLPFC rsFC in PTSD.

Methods: The participants included 21 patients with current PTSD, 30 trauma-exposed non-PTSD (TENC), and 36 non-trauma exposed controls (HC). Whole-brain rsFC analyses from bilateral DLPFC seeds were performed in CONN 15.h. Participants completed the Clinician-Administered PTSD Scale (CAPS) as well as a fear conditioning paradigm.

Results: We found significant group differences in right DLPFC-precuneus rsFC. Compared to both HC and TENC groups, the PTSD group demonstrated increased negative rsFC between these regions. Greater negative right DLPFC-precuneus connectivity was associated with greater precuneus cortical thickness. Within the PTSD group, greater negative connectivity was associated with higher total CAPS scores, driven by higher re-experiencing ($r = -0.546$, $p = 0.016$) and avoidance ($r = -0.444$, $p = 0.057$) but not hyperarousal symptoms ($r = 0.098$, $p = 0.690$). Within the PTSD group, right DLPFC-precuneus connectivity also was associated with skin conductance responses to conditioned stimuli during fear conditioning.

Conclusions: Compared to both TENC and HC, PTSD demonstrated increased right DLPFC-precuneus rsFC, consistent with models suggesting that suppression of cognitive control regions may arise in the context of increased self-referential processing.

Supported By: R01MH096987 (NIMH: Rosso)

Keywords: PTSD - Posttraumatic Stress Disorder, Resting State Functional Connectivity, DLPFC, Fear Conditioning

ORAL SESSION
Development
3:00 p.m. – 5:00 p.m.
Chair: Alicia Smith

O25. Variance in Dopaminergic Markers: A Possible Marker of Individual Differences in IQ?

Jakob Kaminski[1], Florian Schlagenhauf[2], Michael Rapp[3], Swapnil Awasthi[1], Barbara Ruggeri[4], Lorenz Deserno[5], Daedelow Laura[1], Tobias Banaschewski[6], Arun Bokde[7], Erin Burke Quinlan[9], Christian Büchel[9], Uli Bromberg[9], Sylvane Desrivières[8], Herta Flor[7], Vincent Frouin[10], Hugh Garavan[11], Penny Gowland[12], Bernd Ittermann[13], Jean-Luc Martinot[14], Marie-Laure Paillere Martinot[15], Frauke Nees[6], Dimitri Papadopoulos Orfanos[10], Tomas Paus[16], Luise Poustka[7], Michael Smolka[17], Juliane Fröhner[17], Henrik Walter[1], Robert Whelan[7], Stephan Ripke[18], Gunter Schumann[9], and Andreas Heinz[1], IMAGEN Consortium

[1]Charité - University Medical Center Berlin, [2]Charité - University Medical Center Berlin, Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, [3]University of Potsdam, [4]Institute of Psychiatry, Psychology & Neuroscience, King's College London, [5]University of Leipzig, [6]Heidelberg University, [7]Trinity College Dublin, [8]King's College London, [9]Desrivières University Medical Centre Hamburg-Eppendorf, [10]Neurospin, Commissariat à l'Energie Atomique, [11]University of Vermont, [12]University of Nottingham, [13]Physikalisch-Technische Bundesanstalt (PTB), [14]INSERM, [15]APHP, [16]Rotman Research Institute, [17]Technische Universität Dresden, [18]Massachusetts General Hospital

Background: Although intelligence is thought to be heritable, there is evidence for environmental effects on cognitive performance as evidenced by a strong increase in average intelligence in the second half of the previous century (Flynn-Effect). It is highly suggestive that environmental factors interact with genotype by regulation of gene expression and thus contribute to individual malleability. This might be reflected in recent observations of an association between the dopamine-dependent encoding of reward prediction errors and intelligence, which was modulated by environmental factors.

Methods: In a sample of 1475 young healthy adolescents from the IMAGEN cohort, general IQ was assessed. As predictors, we used polygenic scores for intelligence, methylation count in CpG-islands relevant for dopaminergic neurotransmission, gray matter in the striatum and brain activation elicited by temporarily surprising reward-predicting cues.

Results: We could show, that IQ is positively associated with 1) polygenic scores for intelligence (3.2% of variance explained, p=7.3x10-8), 2) epigenetic modification of DRD2 gene (2.7%, p=3.2x10-4), 3) gray matter density in the striatum (0.71%, p=1.7x10-3), and 4) functional activation during reward anticipation (1.4%, p=4.1x10-6). Comparing the relative importance in an overlapping subsample, our results point to the equal importance of genetic variance, epigenetic modification, as well as functional activation.

Conclusions: Our findings suggest that functional activation of the reward system, epigenetic control of dopaminergic neurotransmission and genetic markers contribute equally to IQ. Peripheral epigenetic markers are in need of confirmation in the central nervous system and should be tested specifically assessing individual and social stress factors that can modify the epigenetic markers.

Keywords: Intelligence, Dopamine, Epigenetic Biomarkers, Reward Anticipation, Polygenic Risk Score

O26. Brain Signatures of Emotional Lability and ADHD Traits in Young Children

Christiane Rohr[1], Amy Webber[1], Dennis Dimond[1], Deborah Dewey[1], and Signe Bray[1]

[1]University of Calgary

Background: 40-50% of children with ADHD present with significant levels of emotional lability, which is associated with poorer outcomes. Characterizing emotional lability in relation to the diagnostic dimensions of inattention and hyperactivity is therefore critical for the development of effective treatments. As a starting point, we here investigated the brain basis of these relationships using functional connectivity (FC) analyses in 58 typically developing children aged 4-7 years.
Methods: Children watched a TV show while fMRI data was acquired, and regional time courses were correlated to estimate FC. Emotional lability was assessed with the Emotion Regulation Checklist; inattention and hyperactivity were assessed with the SNAP-IV Parent Questionnaire. To identify shared and distinct neural pathways, we used data-driven connectome-based predictive modelling to develop models of inattention, hyperactivity and emotional lability from the connectivity data.
Results: Emotional lability scores correlated with both inattention ($r=.68$, $p<0.001$) and hyperactivity scores ($r=.66$, $p<0.001$); inattention and hyperactivity were also correlated ($r=.8$, $p<0.001$). FC associated with all three scores revolved around pathways between midbrain-thalamus and the default mode network. In addition, emotional lability and inattention exclusively shared pathways within the dorsal attention network and its connections to hippocampus and dorsolateral prefrontal cortex; emotional lability and hyperactivity exclusively shared thalamostriatal connections, as well as connections between hippocampus and sensory areas.
Conclusions: Our findings suggest that multiple brain pathways underlie the link between emotional lability and ADHD traits in early childhood. Further, they demonstrate the utility of dimensional (continuous) scores and multivariate predictive modelling to interrogate brain-behavior relationships in young children.
Supported By: Alberta Innovates, NSERC, CIHR-INMHA, Alberta Children's Hospital Foundation, I3T
Keywords: Functional Brain Connectivity, Neural Networks, Individual Differences, ADHD, Emotional Dysregulation

O27. A Role for Bile Acid Signaling in Antipsychotic-Induced Weight Gain

Lauren Seaman[1], Kym Faull[1], James McCracken[1], and Erika Nurmi[2]

[1]University of California, Los Angeles, [2]National Institute of Mental Health & Neurosciences

Background: Weight gain and metabolic syndrome are common and serious treatment-limiting adverse effects of medications commonly used to treat mental illness, especially antipsychotic drugs. Children are at increased risk for these side effects. Despite substantial morbidity and dysfunction, the mechanism of antipsychotic-induced weight gain (AIWG) is poorly understood. Given a growing appreciation for the role of bile acids (BA) in energy balance and hormone regulation, we hypothesized that BA perturbations might contribute to AIWG.
Methods: In a cohort of 30 children (age 4-17) who had initiated and sustained risperidone (RSP) treatment for an 8-week period in the NIMH RUPP RSP trial, blood plasma was collected at baseline and completion. The six most abundant human BA species were assayed with high-performance liquid chromatography tandem mass spectrometry.
Results: We observed marked RSP-induced changes in total BA pool and diversity, predominately in the primary BA species chenodeoxycholic acid (CDCA) and cholic acid (CA), that correlated with AIWG ($p=0.01$). In the subset showing BA change with RSP, the ratio of the change in CDCA to that in ursodeoxycholic acid (UDCA) differentiated those with AIWG ($\Delta CDCA/\Delta UDCA>1$) from those without. This algorithm correctly predicted AIWG status in 11/12 (92%) participants ($p=0.001$), with a sensitivity of 100% and specificity of 86%. Sex, age, race/ethnicity, and RSP dose/plasma level did not impact results.
Conclusions: Our data suggests that antipsychotics impact BA pathways and that alterations to the BA balance may contribute to AIWG. BA ratios can act as a biomarker to predict AIWG and may suggest future therapeutics.
Supported By: NIH
Keywords: AIWG, Bile Acids, Antipsychotics, Mass Spectrometry, Metabolic Side Effects

O28. Differential Development Impacts of Different Sub-Types of Abuse and Neglect on Systems Engaged in Task Performance and Emotional Responding

James Blair[1], Karina Blair[1], Joseph Aloi[2], Stuart White[1], Harma Meffert[3], Patrick Tyler[3], Laura Thornton[1], Brittany Taylor[1], Emily Leiker[1], Shah Niraj[1], Heba Abdel-Rahim[1], and Kayla Pope[4]

[1]Boys Town National Research Hospital, [2]Center for Neurobehavioral Research, Boys Town National Research Hospital, University of Nebraska Medical Center, [3]Center for Neurobehavioral Research, Boys Town National Research Hospital, [4]Center for Neurobehavioral Research, Boys Town National Research Hospital, Creighton University

Background: Exposure to prior maltreatment has been associated with detrimental developmental impacts. However, there have been recent suggestions that a differentiation should be made between the developmental impact of two different forms of maltreatment: abuse (physical, emotional and sexual) and neglect (physical and emotional). In addition, it is possible that different sub-types of past abuse and neglect differentially impacts brain development. However, little work has been able to directly address this issue.
Methods: In this study, youth in a residential care facility and the surrounding community (N=117) who had experienced

varying levels of prior maltreatment performed the affective Stroop task during fMRI
Results: Increasing levels of prior abuse were associated with specific disruptions in the recruitment of regions implicated in top-down attentional control, including superior frontal cortex BA 8 and posterior cingulate cortex during cognitive trial tasks. In contrast, increasing levels of neglect were associated with a specific disruption in recruitment of bilateral regions of a relatively superior region of anterior insula cortex implicated in attentional processing in the context of threatening distracters. In addition, different subtypes of abuse and in particular emotional abuse and sexual abuse were associated with disruptions specific to that type of abuse.
Conclusions: These data demonstrate the adverse developmental impacts of both abuse and neglect and reveal their developmental specificity for systems engaged in task performance and emotional responding. Further they indicated that different sub-types of abuse are important in future specifications and treatment considerations.
Supported By: Boys Town National Research Hospital, National Institute of all Mental Health
Keywords: Trauma, Development, fMRI

O29. Multi-Modal Imaging Investigation of Anterior Cingulate Cortex Cytoarchitecture in Neurodevelopment

Natalie Forde[1], Jilly Naaijen[2], Marcel Zwiers[2], David Lythgoe[3], Sophie Akkermans[2], Thaira Openneer[4], Jan Buitelaar[2], and Pieter Hoekstra[4]

[1]Center for Addiction and Mental Health, [2]Donders Institute, [3]King's College London, [4]UMCG

Background: Multi-modal imaging may improve our understanding of the relationship between cortical morphology and cytoarchitecture. To this end we integrated the analyses of several magnetic resonance imaging (MRI) and spectroscopy (MRS) metrics within the anterior cingulate cortex (ACC). Considering the ACCs role in neurodevelopmental disorders, we also investigated the association between neuropsychiatric symptoms and the various metrics.
Methods: T1- and diffusion-weighted MRI and 1H-MRS (ACC voxel) data along with phenotypic information were acquired from children (8-12 years) with various neurodevelopmental disorders (n=95) and healthy controls (n=50). From within the MRS voxel mean diffusivity (MD) of the grey matter fraction, intrinsic curvature (IC) of the surface and concentrations of glutamate, N-acetylaspartate, myo-inositol, choline and creatine were extracted. Linear models were used to investigate if the neurochemicals predicted MD and IC or if MD predicted IC. Finally, measures of various symptom severities were included to determine the influence of symptoms of neurodevelopmental disorders.
Results: All five neurochemicals inversely predicted MD (all puncorrected$<$0.04, β=0.23-0.36). There was no association between IC and MD or IC and the neurochemicals (all p$>$0.05). Severity of autism symptoms related inversely to MD (puncorrected=0.002, β=0.39).
Conclusions: Our findings support the notion that the neurochemicals relate to cytoarchitecture within the cortex. Additionally, we showed that autism symptoms across various disorders and healthy participants related to the ACC cytoarchitecture with higher cell density in those with more severe symptoms.
Supported By: European Community's Seventh Framework Programme (FP7/2007-2013) TACTICS grant agreement no. 278948 and (FP7-PEOPLE-2012-ITN) TS-EUROTRAIN grant agreement no. 316978
Keywords: Multimodal Neuroimaging, Autism Spectrum Disorder, Cross-Disorder, Anterior Cingulate Cortex (ACC), Magnetic Resonance Spectroscopy

O30. Frontal EEG Asymmetry in Extremely Low Birth Weight Adult Survivors: Links to Antenatal Corticosteroid Exposure and Psychopathology

John Krzeczkowski[1], Louis Schmidt[1], Calan Savoy[1], Saroj Saigal[1], and Ryan J. Van Lieshout[2]

[1]McMaster University, [2]Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, McMaster University

Background: Extremely low birth weight (ELBW; $<$1000g) survivors are exposed to severe perinatal adversities known to affect neurodevelopment. Many of these individuals are also exposed to antenatal corticosteroids (ACS), which increase neonatal survival, but may alter neurodevelopmental trajectories in the long-term. However, the neurophysiological outcomes of adults born ELBW and exposed to ACS are unknown.
Methods: Resting frontal electroencephalogram (EEG) alpha asymmetry was compared between ELBW survivors [n=51, of which n=23 were exposed to ACS (ELBW-S), and n=28 were not exposed (ELBW-NS)] and normal birth weight controls (NBW; n=66) in adulthood (mage=32.3 years) in the oldest known prospectively followed cohort of ELBW survivors in the world.
Results: Greater relative right frontal EEG alpha asymmetry at rest was observed in ELBW survivors relative to NBW controls (MELBW=-0.18, SE=0.07; MNBW=0.04, SE=0.06, F(1,115)=2.3, p=0.03). Additionally, a linear relation was observed for those exposed versus those not exposed to antenatal steroids, such that the highest levels of right frontal asymmetry were observed in ELBW-S versus the ELBW-NS versus NBW adults (r=0.2, p=0.029). Greater right frontal asymmetry was associated with increased psychopathology in all individuals.
Conclusions: ELBW survivors exhibit frontal brain activity patterns that are linked to an increased risk of psychopathology in adulthood. The subset of ELBW survivors who were also exposed to ACS appear to be at even greater risk. Given that resting right frontal brain activity is a known risk factor for mental disorders, it may be of benefit to monitor the mental

health of ELBW survivors, particularly those exposed to ACS into adulthood.
Supported By: CIHR
Keywords: Electroencephalography (EEG), Extremely Low Birthweight, Psychopathology, Perinatal Steroids, Frontal EEG Asymmetry

O31. Age-Normative Pathways of Striatal Connectivity Relate to ADHD Symptoms in the General Population

Anita Barber[1], Deepak Sarpal[2], Majnu John[1], Christina Fales[1], Anil Malhotra[3], Katherine Karlsgodt[4], and Todd Lencz[3]

[1]Feinstein Institute, [2]University of Pittsburgh Medical Center, [3]Hofstra Northwell School of Medicine, [4]UCLA

Background: Altered striatal development contributes to core deficits in motor and inhibitory control, impulsivity, and inattention associated with ADHD. Previous studies examining the development of striatal connectivity do not adequately sample various developmental stages to assess both linear and nonlinear age effects.
Methods: Resting state fMRI and T1-weighted scans were collected for the Pediatric, Imaging, Neurocognition and Genetics (PING) study and the Philadelphia Neuroimaging Cohort (PNC). 1215 neurotypical participants (ages 3-22 years) had usable resting-state data. Six 4-mm seeds were placed in striatal subdivisions in each hemisphere. Models assessed linear and nonlinear age effects and accounted for Frame-wise Displacement (FD), FD-squared, and site. A growth-charting approach was applied to the Developing Striatal Connections (DSCs). Age-deviation scores were computed from the 50th percentile (i.e. age-normative) fit line and Principal Component Analysis (PCA) was performed to identify age-normative patterns of striatal connectivity.
Results: PCA on the age deviation scores from the set of DSCs revealed four striatal pathways of normative development. Using permutation testing (10,000 permutations), associations were found between PCA component 2 and ADHD measures (ADHD liability: $\beta = 0.014$, $p = 0.0032$; inattention: $\beta = 0.020$, $p = 0.0016$).
Conclusions: Age-normed striatal connectivity related to ADHD symptoms and reflected delayed development for several intra-striatal and striatal-cerebellar connections, but accelerated development for a few intra-caudate and striatal-posterior OFC connections. Developmental overreactivity in this limbic circuitry could underlie reward reactivity, impulsivity, and poor emotion regulation associated with ADHD.
Supported By: PNC funding: Support for the collection of the data sets was provided by grant RC2MH089983 awarded to Raquel Gur and RC2MH089924 awarded to Hakon Hakonarson. All subjects were recruited through the Center for Applied Genomics at The Children's Hospital in Philadelphia.

* PING funding: Data collection and sharing for this project was funded by the Pediatric Imaging, Neurocognition and Genetics Study (PING) (National Institutes of Health Grant RC2DA029475). PING is funded by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health & Human Development. PING data are disseminated by the PING Coordinating Center at the Center for Human Development, University of California, San Diego.
Keywords: Neurodevelopmental Disorders, Corticostriatal, ADHD, Resting State Functional Connectivity, Brain Imaging, fMRI

O32. Caregiving Impacts Infant Emotionality and Neural Network Topology

Lindsay Hanford[1], Vincent Schmithorst[2], Ashok Panigrahy[2], Vincent Lee[2], Julia Ridley[3], Lisa Bonar[1], Amelia Versace[1], Alison Hipwell[3], and Mary Phillips[1]

[1]University of Pittsburgh, [2]Children's Hospital of Pittsburgh of UPMC, [3]UPMC

Background: Little is known regarding the extent to which neural networks underlying emotional reactivity and regulation in infancy serve as precursors of later behavioral and emotional problems. Even less is known about caregiving influences on these early brain-behavior relationships. To investigate this, we employed graph theory techniques to examine the underlying neural network topology related to emotional behaviors in infancy, and further determine the moderating effects of caregiving on these brain-behavior relationships.
Methods: Resting state functional magnetic resonance imaging of the infant, and face-to-face interactions between mother and infant, were collected on 48 dyadic pairs. Behavioral indices of emotionality and maternal caregiving were coded by independent observers. Network measures were calculated through graph theory techniques with a focus on two nodal metrics: clustering coefficient (CC), and nodal efficiency (NEff). FDR-corrected mixed-effect general linear models examined the relationships between infant emotionality and nodal measures, and the moderating effects of caregiving.
Results: Our major findings indicate that early maternal mental-state talk, an aspect of maternal caregiving, positively moderates associations between positive emotionality and CC in prefrontal and occipital cortical networks ($pFDR<0.01$). Here, higher levels of maternal mental-state talk are associated with stronger positive relationships between positive emotionality and CC within these networks.
Conclusions: Our findings highlight the critical importance of infant-focused caregiving, beyond positive and negative caregiving, for the establishment of brain-emotional behavior relationships, and point to specific targets for caregiving interventions to positively impact critical brain-emotional behavior relationships, and improve the health and well-being of vulnerable infants.
Supported By: R21
Keywords: Infants, Resting State fMRI, Network Analysis, Emotional Reactivity, Optimal Maternal Caregiving

Saturday, May 12, 2018

ORAL SESSION
Motivation, Reward & Addiction
12:30 p.m. – 2:30 p.m.
Chair: Iliyan Ivanov

O33. Compulsive Addiction-Like Aggressive Behavior in Mice

Sam Golden[1], Conor Heins[1], Michelle Jin[1], Marco Venniro[1], Daniele Caprioli[1], Michelle Zhang[1], David Epstein[1], and Yavin Shaham[1]

[1]National Institute on Drug Abuse

Background: Some people are highly motivated to seek aggressive encounters, and among those who have been incarcerated for such behavior, recidivism rates are high. These observations echo two core features of drug addiction: high motivation to seek addictive substances, despite adverse consequences, and high relapse rates. Here we used established rodent models of drug addiction to determine whether they would be sensitive to "addiction-like" features of aggression in CD-1 mice.
Methods: In Exp. 1-2, we trained older CD-1 mice to lever-press for opportunities to attack younger C57BL6/J mice. We then tested them for relapse to aggression seeking after forced abstinence or punishment-induced suppression of aggression self-administration. In Exp. 3, we trained a large cohort of CD-1 mice, and tested them for choice-based voluntary suppression of aggression seeking, relapse to aggression seeking, progressive ratio responding, and punishment-induced suppression of aggression self-administration. We then used cluster analysis to identify patterns of individual differences in compulsive "addiction-like" aggressive behavior.
Results: In Exp. 1-2, we observed strong motivation to acquire operant self-administration of opportunities to aggress, and relapse vulnerability during abstinence. In Exp. 3, cluster analysis of the aggression-related measures identified a subset of "addicted" mice (~19%) that exhibited intense operant-reinforced attack behavior, decreased likelihood to select an alternative reinforcer over aggression, heightened relapse vulnerability and progressive ratio responding, and resilience to punishment-induced suppression of aggressive behavior.
Conclusions: Using procedures established to model drug addiction, we showed that a subpopulation of CD-1 mice demonstrate "addiction-like" aggressive behavior, suggesting an evolutionary origin for pathological aggression.
Supported By: NIGMS 1FI2GM117583-01
Keywords: Aggression, Reward, Motivation, Relapse, Addiction

O34. Stress Modulates the Subjective Cost of Exercising Self-Control

Candace Raio[1] and Paul Glimcher[1]

[1]New York University

Background: Emerging accounts propose that deviations from goal-directed behavioral control may arise from a rational decision-making process that weighs the costs and benefits of exercising cognitively demanding control. Here, we measured individuals' subjective control costs in the presence of temptation and tested how acute stress–widely known to compromise behavioral control–changes these estimated costs.
Methods: We employed a novel economic decision-making task in which healthy dieters reported their willingness-to-pay to eliminate the presence of a tempting food reward over time, allowing us to measure their subjective cost of exercising self-control. We tracked how these costs differed in participants who were physiologically stressed (cold-pressor) beforehand, as confirmed by salivary cortisol elevations.
Results: Across two separate studies (each N=63), participants were willing to pay ~30% of their monetary endowment to restrict exposure to temptation, confirming that we can measure the cost of exercising control in humans. In Study 1, stressed participants (N=31) paid significantly more than controls to avoid temptation, suggesting that stress-related deficits in behavioral control may stem from higher control costs under stress (t-test: $t(61)=2.65$, $p<.01$). In Study 2, introducing monetary incentivizes to exercise control reversed this effect, such that stressed participants reported lower control costs to avoid temptation ($t(61)=-2.11$, $p<.05$).
Conclusions: Consistent with an emerging framework viewing behavioral control as a cost-benefit decision, these data suggests that individuals' subjective control costs can be quantified and are highly sensitive to stress exposure and incentive motivation. These findings may open new avenues of research investigating how reducing subjective control costs can promote more adaptive decision-making.
Supported By: F32MH110135 to CMR; NARSAD (Brain and Behavior Research Foundation)
Keywords: Self-Control Networks, Effort-Based Decision-Making, Stress exposure, Goal-Directed Control

O35. Understanding the Motivational Side of Placebo Effects: Placebos Enhance Reward Sensitivity on the Neural and Behavioral Level

Liane Schmidt[1], Vasilisa Skvortsova[1], Pierre Chandon[2], Bernd Weber[3], Mathias Pessiglione[1], and Hilke Plassmann[2]

[1]INSERM, [2]INSEAD, [3]Imaging Life & Brain Center Bonn

Background: Recent research from neuroscience suggests that motivational processes are recruited under placebo effects. Here we asked where in the brain and how motivational processes contribute to the occurrence of placebo effects in healthy subjects.
Methods: We used data from two different, but complementary studies. Both studies assessed how labels, that suggest positive effects of drinks, change non-aversive behavior. In study 1 functional magnetic resonance imaging (fMRI) assessed the link between the brain's reward sensitivity and label-based placebo effects on taste pleasantness ratings. In study 2 behavioral testing and cost-benefit computational modeling (N=282) assessed how reward and cost sensitivity determined label-based placebo effects on cognitive effort.
Results: fMRI revealed that the brain's valuation system (ventromedial prefrontal cortex (vmPFC), ventral striatum) formally mediated the effect of price labels on taste pleasantness ratings ($p<0.05$, bootstrap test). This effect was moderated in strength by the vmPFC's sensitivity to task-independent monetary rewards. Study 2 revealed that the label of an energy drink (EnD), but not the actual drink facilitated cognitive effort in high incentive trials only ($p = .001$, Cohen's $d=0.46$). Computational modeling revealed that the EnD label shifted a cost-benefit optimization process toward enhanced reward sensitivity ($p = .002$, Cohen's $d=0.31$) without changing subjects' sensitivity to the cost of effort allocation ($p = .56$, Cohen's $d=0.02$).
Conclusions: These results provide convergent neural, and behavioral evidence that motivational processes via enhanced reward sensitivity facilitate placebo effects in healthy subjects. Our findings open the window toward a better understanding of the neurocognitive processes underpinning placebo effects across behavioral domains.
Keywords: Placebo Effects, Incentive Motivation, Reward Sensitivity Theory

O36. Genetic Overlap and Causality Among Major Depressive Disorder, Alcohol Dependence, and Alcohol Consumption: Findings From the Psychiatric Genomics Consortium

Renato Polimanti[1], Roseann Peterson[2], Raymond Walters[3], Jue-Sheng Ong[4], Stuart MacGregor[4], Alexis Edwards[2], Toni Clarke[5], Josef Frank[6], Zachary Gerring[4], Nathan Gillespie[2], Penelope Lind[4], Hermine Maes[2], Hamdi Mbarek[7], Yuri Milaneschi[8], Fabian Streit[6], Arpana Agrawal[9], Howard Edenberg[10], Kenneth Kendler[2], Patrick Sullivan[11], Naomi Wray[4], Joel Gelernter[12], and Eske Derks[4]

[1]Yale University School of Medicine, [2]Virginia Commonwealth University, [3]Broad Institute of MIT and Harvard, [4]QIMR Berghofer Medical Research Institute, [5]University of Edinburgh, [6]University of Heidelberg, [7]Vrije Universiteit Amsterdam, [8]VU University Medical Center, [9]Washington University in St. Louis, [10]Indiana University School of Medicine, [11]University of North Carolina, [12]Yale University

Background: Despite epidemiological and genetic reports on the association between major depressive disorder (MDD) and alcohol dependence (AD), there has been limited research on the nature of causality with respect to these psychiatric disorders. Here, we used the latest results from the Psychiatric Genomics Consortium to dissect genetic overlap and causality among major depressive disorder, alcohol dependence, and alcohol consumption.
Methods: Linkage Disequilibrium score regression and two-sample Mendelian randomization (MR) were applied to summary statistics of genome-wide association studies of MDD, AD, and alcohol consumption (frequency, ACF, and quantity, ACQ) from the Psychiatric Genomics Consortium and UK Biobank.
Results: AD showed significant positive genetic correlations with MDD ($rg=0.47$, $p=6.70\times10\text{-}11$) and ACQ ($rg= 0.75$, $p=1.2\times10\text{-}13$). There was a significant positive genetic correlation between ACF and ACQ ($rg= 0.54$, $p=3.8\times10\text{-}170$), but MDD nevertheless showed significant genetic correlations with these two traits in opposite directions (ACF: $rg=-0.17$, $p=2.43\times10\text{-}11$; ACQ: $rg= 0.14$, $p=4.8\times10\text{-}7$). The MR analysis indicated that most of these correlations are best explained by shared genetic mechanisms, but a strong causal relationship is present between MDD and AD as individuals with a lifetime MDD diagnosis have a 32% increased risk of having a lifetime AD diagnosis ($beta=0.28$, $p=1.29\times10\text{-}6$).
Conclusions: Results indicate that comorbidity among MDD, AD, and AC is partially due to shared genetic liability, and partially to causal mechanisms of MDD predisposing to AD. The current findings have important implications for both MDD and AD treatment and prevention efforts as well as understanding mechanisms involved in the etiology of psychiatric comorbidities.
Supported By: NIH U01 MH109532; NIH U01 MH109528
Keywords: Comorbidity, Psychiatric Genetics, Genome-Wide Association Data

O37. Altered Aversive Interoceptive Anticipation and Processing in Women Remitted From Bulimia Nervosa: Time-Course and Connectivity Findings

Laura Berner[1], Alan Simmons[2], Christina Wierenga[2], Amanda Bischoff-Grethe[1], Martin Paulus[3], Ursula Bailer[4], Miki Ogasawara[1], and Walter Kaye[1]

[1]University of California, San Diego, [2]University of California, San Diego/San Diego VA Healthcare System, [3]Laureate Institute for Brain Research, University of California, San Diego, [4]Medical University of Vienna

Background: Out-of-control binge/purge episodes and high levels of emotional instability suggest that individuals with bulimia nervosa (BN) have difficulty maintaining internal homeostasis. Integral to both physiological state regulation and emotion regulation is interoception, or the detection and integration of body signals. No study of BN has examined the neural anticipation of and response to aversive interoceptive state changes, which could impact learning from body-related experience and maintain maladaptive eating behaviors.

Methods: Women remitted from BN (RBN; n=24) and control women (CW; n=25) underwent fMRI during a cued inspiratory breathing load paradigm.
Results: During breathing load anticipation, RBN relative to CW showed increased activation in bilateral mid-insula, left superior frontal gyrus, bilateral putamen, right dorsal anterior cingulate, left posterior cingulate, and right amygdala, along with increased functional connectivity between right insula and right amygdala (pFWE<0.001). Time-course analyses revealed that RBN BOLD responses in interoceptive processing regions showed an aberrant decline over the course of the aversive experience (pFWE<0.001). Exploratory analyses indicated that hyperactivation and hyperconnectivity during breathing load anticipation were associated with past binge eating and purging frequencies (pFWE<0.05).
Conclusions: This study is the first to show that BN is associated with altered neural activation during anticipation and processing of unpleasant body state changes. Exaggerated predictive signals and an aberrant pattern of adjustment over time to aversive states may help explain why individuals with BN engage in behaviors that result in alternating over- and under-shooting of homeostasis (i.e., binge eating and purging) and could serve as novel, brain-based treatment targets.
Supported By: R01 MH042984, R01 MH092793, F32 MH108311, the Price Foundation, and the Hilda and Preston Davis Foundation
Keywords: Functional MRI, Interoception, Bulimia Nervosa, Functional Connectivity, Time Series Analyses

O38. Resting-State Connectivity Defines Neurobiological Subtypes Underlying Different Cognitive-Emotional Profiles in Cocaine Addiction

Anna Zilverstand[1], Paul Curtin[1], Muhammad Parvaz[1], Conor Liston[2], Nelly Alia-Klein[1], and Rita Goldstein[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Weill Cornell Medical College

Background: We applied data-driven methods to discover neurobiological subtypes of cocaine addiction based on individuals' resting-state brain function alone. We hypothesized that different neurobiological subtypes may be characterized by different cognitive-emotional functioning and different underlying neurobiological mechanisms.
Methods: We acquired a resting-state scan from 42 individuals with Cocaine Addiction and 32 healthy controls. We applied Graph theory methods to extract functional connectivity (Global Efficiency) from 638 brain regions, which were assigned to 16 large-scale brain networks. The average Global Efficiency per brain network was input into an unsupervised classifier (SOM = self-organizing map), which generated a similarity map of the brain connectivity of all participants. Finally, K-centroid clustering was applied to detecting subgroups within this similarity map. We characterized the discovered subtypes on cognitive-emotional functioning [Multidimensional Personality Questionnaire (MPQ-BF)] and clinical characteristics.
Results: We identified four neurobiological subtypes, which separated cocaine users from healthy controls with high accuracy (92%). Within cocaine users, the discovered subtypes differed on capability for self-constraint and reward sensitivity. In 50% of the cocaine users we found low constraint, whereas the other half demonstrated high reward sensitivity (p<0.01, MPQ-BF). The subtype with low constraint showed increased connectivity of the motor network, whereas the subtype with high reward sensitivity demonstrated increased connectivity of the salience network. Both cocaine user subtypes had equally severe, recent and chronic cocaine use.
Conclusions: The discovered cocaine user subtypes differed in regards to the underlying neurobiological mechanisms, but not in terms of addiction severity. These results may therefore have important implications for developing targeted treatments.
Supported By: 1R01DA023579-01A1, 1R21DA034954-01, 1R01DA041528-01, 1R01MH090134-01, NWO Rubicon 446-14-015
Keywords: Addiction, Resting State, Research Domain Criteria (RDoC), Subtypes, Computational Psychiatry

O39. Expectancies and Reinforcement Manipulations of Mood Improvement

Marta Pecina[1], Thandi Lyew[1], Jonathan Wilson[1], Jordan Karp[2], and Alexandre Dombrovski[1]

[1]University of Pittsburgh, [2]University of Pittsburgh Medical Center, Western Psychiatric Institute & Clinic

Background: Treatment expectancy and learning are implicated in placebo analgesia. However, their implication in mood regulation in an experimental setting has received much less attention.
Methods: 17 participants with Major Depressive Disorder (MDD) completed an experiment inside of a scanner, which combined an intravenous administration of two different placebos described as having either fast-acting or conventional "antidepressant" effects. The controls were two no-infusion conditions. Each infusion and no-infusion conditions were paired with two different "reinforcement" schedules of sham neurofeedback (positive and baseline fake brain-signal readouts displayed in a monitor). Briefly, the task included four 32 trial runs, where each trial began with a 10 second timer cue reflecting each infusion (or no infusion) followed by 20 seconds of sham neurofeedback signal of different valance (positive/baseline). Participants rated their expected and actual change in mood after each infusion and neurofeedback period, respectively. The effects of these manipulations on treatment expectancy and mood ratings were examined in mixed-effects logistic regression models.
Results: Treatment expectancy ratings were significantly higher during the infusion compared to the no-infusion condition (Estimate=0.3, S.E.=0.18, p=0.03), especially during the positive sham neurofeedback condition (Estimate=1.2, S.E.=0.2, p=4.16*E-06). Mood ratings during the task were significantly higher during the positive sham neurofeedback condition (Estimate=1.5, S.E.=0.2, p=8.7*E-13), and in

patients with high treatment expectancy ratings (Estimate=0.43, S.E.=0.6, p=0.03), especially under the high expectancy and positive neurofeedback condition (Estimate=0.56, S.E.=0.28, p=0.04).
Conclusions: In patients with depression, antidepressant treatment expectancies interact with unfolding reinforcement. Specifically, mood improves when positive expectancies are confirmed by positive reinforcement.
Supported By: NARSAD, K23
Keywords: Expectancy, Reinforcement Learning, Mood

O40. Attention and Reward-Related Decision-Making Deficits Differentiate Youth With Bipolar Disorder From Healthy Individuals: A Machine Learning Study

Isabelle Bauer[1], Robert Suchting[2], Benson Mwangi[2], Mon-Ju Wu[2], Thomas Meyer[2], Giovana Zunta-Soares[2], and Jair Soares[2]

[1]University Of Texas, [2]McGovern Medical School at The University of Texas Health Science Center at Houston

Background: Our previous work shows that young and old adults with bipolar disorder (BD) display poor reward-associated decision making (RDM). RDM in youth with BD is a largely unexplored research area. This study uses a component-wise gradient (CGB) machine learning algorithm to identify cognitive measures that can accurately differentiate youth with BD from a healthy comparison group.
Methods: 108 healthy controls (HC; 10.36±3.28 yo, 67F) and 119 children and adolescents with BD (13.31±3.02 yo, 52F) completed the CANTAB cognitive battery. Available data was split into two partitions for algorithm training (80%) and testing (20%). The algorithm was tuned using 10-fold cross validation and evaluated using classification accuracy and area under the receiver operating characteristic curve (AUROC). Algorithm training provided variable selection and measures of variable importance for model interpretation.
Results: After algorithm tuning, CGB achieved accuracy of 73.2% and an AUROC of 0.785 in classifying individuals as either BD or non-BD on a held-out data set for testing. The strongest cognitive predictors of BD were selective and sustained attention, RDM deliberation time, and quality of RDM.
Conclusions: Performance on attention and RDM tasks differentiate youth with BD from HC. This finding will need to be replicated in independent cohorts for generalization purposes. Further studies in high-risk individuals are needed to determine whether deficits in these cognitive domains are related to the disorder or are markers of vulnerability to BD.
Supported By: NIMH
Keywords: Bipolar Disorder, Reward Processing, Children and Adolescence, Machine Learning

ORAL SESSION
Depression & Psychosis
3:00 p.m. – 5:00 p.m.
Chair: Dan Iosifescu

O41. CREB-Zfp189 Interactions Regulate a Resilient-Specific Transcriptional Network in Animal Models of Depression

Zachary Lorsch[1], Peter Hamilton[1], Ashley Lepack[1], Philipp Mews[1], Eric Parise[1], Lyonna Alcantara[1], Orna Issler[1], Aarthi Ramakrishnan[1], Immanuel Purushothaman[1], Yong-Hwee E. Loh[1], Andrew McKenzie[1], Minghui Wang[1], Ian Maze[1], Bin Zhang[1], Li Shen[1], Rosemary Bagot[2], and Eric Nestler[1]

[1]Icahn School of Medicine at Mount Sinai, [2]McGill University

Background: Major Depressive Disorder (MDD) is associated with abundant transcriptional alterations. RNA sequencing studies in animal depression models corroborate these findings, but find quantitatively more changes in stress resilient animals. Despite this, most studies of resilience have focused on single genes, and the mechanism by which sets of genes interact to induce resilience is currently unknown.
Methods: To address this, we performed weighted gene co-expression network analysis (WGCNA) on RNA transcripts following 10 days of chronic social defeat stress (CSDS).
Results: We identified a network of genes unique to the resilient phenotype. Zfp189, which encodes a previously uncharacterized zinc finger protein, was the most connected gene in this resilient-specific network and was differentially expressed in the prefrontal cortex (PFC) of resilient mice. Consistent with these findings, Zfp189 overexpression in mouse PFC was both pro-resilient and antidepressant, and RNA sequencing of virally infected tissue showed preferential changes in the network from which Zfp189 originates. We found that CREB is a predicted upstream regulator of our resilient network and ChIP-chip data found that CSDS decreased CREB binding to Zfp189, a phenomenon that was reversed by the antidepressant imipramine. Accordingly, knockout of CREB in the PFC increased susceptibility to stress, but the deleterious effects of CREB knockout were ablated by Zfp189 overexpression. Additionally, we utilized CRISPR to direct activated CREB to the Zfp189 locus in the PFC, and this too was sufficient to increase resilience.
Conclusions: These findings suggest that CREB interacts with Zfp189 to regulate a resilient-specific transcriptional network in PFC that induces behavioral resilience.
Supported By: NIHF30MH110073, NIHP50MH096890, Hope for Depression Research Foundation
Keywords: Major Depressive Disorder (MDD), Transcriptomics, Gene Networks, CREB, Antidepressant Response

O42. Gene-Environment Correlation Does not Explain Away the Association Between Childhood Trauma and Psychopathology: A Monozygotic Twin Differences Approach

Aleksandra Lecei[1], Jeroen Decoster[1], Marc De Hert[1], Catherine Derom[2], Noortje Jacobs[3], Claudia Menne-Lothmann[3], Jim van Os[4], Evert Thiery[2], Bart Rutten[3], Marieke Wichers[3], and Ruud van Winkel[1]

[1]KU Leuven, [2]Ghent University, [3]Maastricht University, [4]UMC Utrecht

Background: It is generally assumed that childhood trauma (CT) is a causal risk factor for psychopathology. However, studies have shown that baseline psychopathology may actually increase risk for subsequent victimization, suggesting that exposure to CT is not random but may result from pre-existing vulnerability. Therefore, studies testing whether the association between CT and psychopathology persists when accounting for gene-environment correlation are much needed.
Methods: A monozygotic (MZ) twin differences approach was used to examine whether differences in CT exposure among MZ twin pairs would be associated with MZ differences in symptoms. As MZ twins are genetically identical, within-pair correlations between CT exposure and psychopathology would rule out the possibility that the association is solely attributable to gene-environment correlation. 146 monozygotic twin pairs (n=292) recruited from the general population were selected for this study.
Results: In the whole sample, CT was associated with symptoms of psychopathology (B=43.13; SE=6.27; p<.001). There were meaningful differences within MZ twin pairs in CT exposure and symptoms. These within-pair differences in CT exposure were associated with within-pair differences of overall psychopathology (B=29.22; SE=12.24; p=.018) as well as specifically symptoms of anxiety (B=0.65; SE=0.21; p=.002), depression (B=0.37; SE=0.18; p=.043), and psychosis (B=0.35; SE=0.16; p=.024).
Conclusions: While it is not unlikely that pre-existing vulnerability may increase the risk for traumatic exposures, such gene-environment correlation does not explain away the association between CT and psychopathology. The present findings thus suggest that at least part of the association between CT and psychopathology may be causal.
Supported By: Other
Keywords: Childhood Trauma, Twins, Gene X Environment, Psychopathology

O43. Cognitive and Emotional Biomarkers of Anxious Major Depressive Disorder: An iSPOT-D Report

Taylor Braund[1], Donna Palmer[2], Leanne M. Williams[3], Amit Etkin[4], and Anthony Harris[1]

[1]Brain Dynamics Centre, Westmead Institute for Medical Research and Discipline of Psychiatry, Sydney Medical School, University of Sydney, [2]The Brain Resource Company, [3]Stanford University & Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC) VA Palo Alto Health Care System, [4]Stanford University School of Medicine, Stanford Neurosciences Institute, Veterans Affairs Palo Alto Healthcare System

Background: Major depressive disorder (MDD) commonly co-occurs with one or more anxiety disorders or with clinically significant levels of anxiety symptoms. While evidence suggests these anxious forms of MDD present with more severe clinical profiles and are prognostic of poorer antidepressant treatment outcomes, little is known of their cognitive and emotional functioning. We compared cognitive and emotional functioning in various forms of anxious MDD and assessed whether functioning could predict antidepressant treatment outcome.
Methods: 1,008 adults with MDD and 336 healthy controls completed IntegNeuro: a computerized cognitive and emotional functioning assessment battery. Participants were then randomised to one of three antidepressants and reassessed at 8 weeks regarding 17-item Hamilton Depression Rating Scale (HRSD17) and 16-Item Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR16) remission and response. Anxious MDD was defined using common criteria (i.e., MDD with one or more anxiety disorders, or a HRSD17 Anxiety subscale score > 7) and theoretically driven novel criteria (i.e., MDD with severe/extremely severe Depression Anxiety Stress Scales (DASS) Anxiety and Stress subscale scores).
Results: Syndromal anxious MDD had poorer working memory, HRSD anxious MDD had better emotion identification, and DASS anxious MDD had poorer working memory and cognitive flexibility compared to their non-anxious counterparts. Baseline functioning in people with HRSD anxious MDD also predicted QIDS-SR16 response (74% cross-validated accuracy).
Conclusions: Cognitive and emotional functioning in anxious MDD varied depending on its definition, but generally compounded existing MDD deficits with anxiety related deficits (i.e., executive functions). Subtyping by anxious MDD can also help develop cognitive and emotion-based treatment prediction biomarkers.
Supported By: The Brain Resource Company, NSW Health PhD Scholarship
Keywords: Major Depressive Disorder (MDD), Anxiety, Cognition, Emotion

O44. Effort and Reward Evaluation in Remitted Depression: A Preliminary Report on a Possible Predictor of Relapse

Isabel Berwian[1], Inga Schnuerer[1], Julia Wenzel[2], Daniel Renz[1], Klaas Stephan[3], Henrik Walter[2], and Quentin Huys[4]

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Background: Relapse after antidepressant medication (ADM) discontinuation is high (30% in 6 months) and no established predictors exist. The role of anhedonia, one of the core

symptoms of depression, in relapse is also unclear. Furthermore, whether the symptoms reflecting anhedonia result from reduced sensitivity to reward or increased sensitivity to effort has not been disentangled yet.
Methods: As part of a longitudinal patient study, we conducted a physical effort task in remitted, previously depressed, patients and matched healthy controls (HC). The patient sample discontinued their ADM after the measurement and was followed up for 6 months to assess relapse. We compared computational models to differentiate between the relative impact of rewards and effort.
Results: Our preliminary results indicate that patients (n=64) showed a significantly decreased willingness to invest effort for small rewards compared to HC (n=22) ($p<0.0001$). The behavioural differences between patients and HC was captured by a significant difference of effort sensitivity ($p=0.005$) in the most parsimonious model. Moreover, compared to HC, patients took longer to decide about investing more effort for high rewards ($p=0.041$) and decreased their investment over time on more ambiguous trials ($p=0.049$). A similar pattern of results emerged when comparing patients who relapsed (n=13) and who did not relapse (n=19) after ADM discontinuation, though this did not reach significance ($p=0.22$).
Conclusions: We provide evidence for a trait marker of depression, namely increased effort sensitivity. This marker shows potential as predictor for relapse after ADM discontinuation.
Supported By: Swiss National Science Foundation project grant to Q.J.M.H. (320030L_153449/1), Molecular Imaging Network Zurich (MINZ), René and Susanne Braginsky Foundation, German Research Foundation (DFG), Transregional Collaborative Research Center 134
Keywords: Relapse Prediction, Effort-Based Decision-Making, Remitted Depression, Computational Psychiatry

O45. Amygdala-Prefrontal Coupling as a Marker for Depression Vulnerability, Resilience, and Pathology

Carolin Wackerhagen[1], Ilya Veer[1], Susanne Erk[1], Sebastian Mohnke[1], Wüstenberg Torsten[1], Nina Romanczuk-Seiferth[1], Andreas Meyer-Lindenberg[2], Andreas Heinz[1], and Henrik Walter[1]

[1]Charite University Medical Center Berlin, [2]Central Institute of Mental Health, University of Heidelberg, Mannheim

Background: Cortico-limbic dysregulation is a leading neurobiological model of major depressive disorder (MDD), but its role in the pathogenesis of MDD is still unclear. We previously reported altered amygdala-prefrontal functional connectivity (FC) in subjects at familial risk for depression, which we discussed as either a marker of vulnerability or resilience. Here, we compared amygdala FC of the at-risk relatives with a newly acquired sample of MDD patients and controls, aiming to disentangle biomarkers of vulnerability/compensation and pathology.
Methods: Amygdala FC during a faces matching task was assessed using fMRI, and compared between relatives, MDD patients, and healthy controls (N=311). Amygdala FC was assessed across and between task conditions. Subsamples matched for age and sex were generated to a) assess task-dependent changes of amygdala FC between patients and controls, and b) compare relatives, MDD patients and controls.
Results: Our previously reported task-dependent changes of amygdala FC across groups were replicated in the new sample. Across faces processing, relatives showed increased amygdala FC with the perigenual anterior cingulate cortex (pgACC) compared to MDD patients and controls. MDD patients showed reduced amygdala FC with pgACC and precuneus compared to both relatives and controls (all results $p<.05$, whole-brain FWE corrected).
Conclusions: Our results show robust task-dependent changes in amygdala FC during implicit emotion processing. Increases in amygdala-pgACC FC in relatives may play a protective role, while decreased amygdala FC with pgACC and precuneus in MDD patients may reflect a marker of pathology. These results might contribute to a personalized prognosis of depression risk/resilience in the future.
Supported By: German Federal Ministry for Education and Research (BMBF), grant numbers O1ZX1314B and O1ZX1314G
Keywords: Amygdala, Functional Connectivity, Major Depression, Familial Risk, Resilience and Vulnerable

O46. SAGE-217 a First in Class GABAA Receptor Positive Allosteric Modulator in Major Depressive Disorder: A Multicenter, Randomized, Double-Blind, Phase 2 Placebo-Controlled Trial

Handan Gunduz-Bruce[1], Christopher Silber[1], Anthony Rothschild[2], Robert Riesenberg[3], Abdul Sankoh[1], Haihong Li[1], Ella Li[1], Charles Zorumski[4], David Rubinow[5], Steven Paul[1], Jeffrey Jonas[1], James Doherty[1], and **Stephen Kanes**[1]

[1]Sage Therapeutics, [2]University of Massachusetts Medical School and UMass Memorial HealthCare, [3]Atlanta Center for Medical Research, [4]Washington University of St. Louis, [5]University of North Carolina at Chapel Hill

Background: This randomized double-blind, placebo-controlled clinical trial evaluated the anti-depressant efficacy and safety of SAGE-217, a positive allosteric modulator of GABAA receptors, in subjects with moderate-to-severe Major Depressive Disorder (MDD).
Methods: Female and male subjects (N=89) ages 18-65 with unipolar depression and a 17-item Hamilton Rating Scale for Depression (HAM-D) total score $\geq$22 were randomized 1:1 to receive SAGE-217 Capsule 30 mg or placebo for 14 days. The primary endpoint was reduction in HAM-D total score versus placebo on Day 15. The Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression-Improvement (CGI-I) were also examined. Pharmacokinetic data were collected. Adverse events (AEs) and other safety measures were obtained through Day 42.

Results: The SAGE-217 group showed significantly greater mean reduction from baseline in HAM-D total score on Day 15 vs placebo (17.6 for SAGE-217 versus 10.7 for placebo; $p<0.0001$). Statistically significant improvements in HAM-D score were first observed on Day 2 ($p=0.0223$) and were present on Day 15 ($p<0.0001$) and Day 28 ($p=0.0243$). Significant improvements were observed for the MADRS, HAM-A, and CGI-I versus placebo. There were no serious or severe AEs. The most common AEs (≥5%) in the SAGE-217 group were headache, nausea, dizziness, and somnolence.
Conclusions: The early, robust, and sustained (over study period) improvements observed in this first placebo-controlled trial of SAGE-217 suggest that positive allosteric modulation of GABAA receptors represents a viable path for investigation in the treatment of MDD and support further development of SAGE-217 in this indication.
Supported By: This study was funded by Sage Therapeutics, Inc.
Keywords: GABA-A, Major Depressive Disorder (MDD), SAGE-217, Positive Allosteric Modulator

O47. Anxiety During Ketamine Infusions Predicts Negative Treatment Responses in Patients With Major Depression

Malek Bajbouj[1], Matti Gärtner[1], Laura Basso[2], Christian Otte[1], Katja Wingenfeld[1], Woo Ri Chae[1], Isabella Heuser-Collier[1], Francesca Regen[1], Nicoleta Carmen Cosma[1], Simone Grimm[1], and Sabine Aust[1]

[1]Charité, [2]University Hospital Zurich

Background: About 20 to 30 percent of patients with Major Depressive Disorder (MDD) do not respond to standard treatment and are considered treatment-resistant. The N-methyl-Daspartate (NMDA) glutamate receptor antagonist ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant MDD, but it is unknown whether acute psychological effects of ketamine predict the later antidepressant effect. Therefore, we investigated the association between antidepressant responses to ketamine and ketamine-induced psychological experiences in MDD patients.
Methods: A total of 31 patients ($M=49.5\pm11.2$ years, 16 women) with MDD were treated with three ketamine infusions per week (0.5mg/ kg over 40 min) administered for two consecutive weeks. Depression severity was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, four and 24 hours after the first and last infusion. The 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) was applied four hours after the first infusion to assess acute psychological effects.
Results: After six infusions on average, 17 of 31 patients (55%) showed a response (50% MADRS reduction) with 10 patients (32%) fulfilling the criteria of remission, while 14 patients (45%) had no response. Anxious ego-disintegration including experiences of negative derealization and loss of body-/self-control during the first ketamine infusion was negatively predictive of the treatment response ($p<.005$). Positive experiences were not associated with responses to ketamine.
Conclusions: The study demonstrated the considerable impact of anxiety-related ketamineinduced alterations of consciousness on the antidepressant efficacy of ketamine. It underpins the importance of considering patients' subjective experiences and underlines the possibility of a phenotypic response predictor. (ClinicalTrials.gov Identifier NCT02099630)
Keywords: Depression, Ketamine, Phenotyping, Antidepressant Response

O48. White Matter Predictors of Risk for Anhedonic PTSD Symptoms

Negar Fani[1], Jennifer Stevens[1], Sanne van Rooij[1], Cherita Clendinen[1], Tanja Jovanovic[1], Barbara Rothbaum[2], Kerry Ressler[3], and Vasiliki Michopoulos[1]

[1]Emory University, [2]Emory University School of Medicine, [3]McLean Hospital

Background: Three symptoms of PTSD— feelings of detachment from others, diminished positive affect, and decreased interest in activities—reflect anhedonia, or the inability to feel pleasure. Little is known about how these symptoms emerge; however, lines of depression research suggest that changes in particular white matter structures influence the development of anhedonia. The present study investigated how the integrity of white matter pathways at the time of trauma may increase susceptibility to future post-traumatic anhedonia (PTA) symptoms.
Methods: Thirty men and women ($Mean=33.7$, $SD=12.5$) were recruited from the emergency department of a level 1 trauma center; they received diffusion tensor imaging at approximately 1 month and clinical assessments at 6 months post-trauma. Logistic regression was conducted to examine white matter tract integrity as a predictor of PTA after accounting for clinical risk factors.
Results: Logistic regression results indicated that, after accounting for early PTSD symptoms (at one month) and other clinical risk factors, the integrity of the uncinate fasciculus uniquely predicted the presence of PTA at six months post-trauma ($Beta=-225.6$, $p<.05$). Together, these factors contributed to 76% of the variance in PTA.
Conclusions: Our findings indicate that the integrity of the uncinate fasciculus at the time of trauma may directly affect vulnerability for the development of PTA symptoms, even after accounting for clinical risk factors. We will discuss the salience of the uncinate fasciculus for the development of anhedonic symptoms of PTSD, and the results of a replication in a separate prospective study sample.
Supported By: NIMH
Keywords: Diffusion Tensor Imaging (DTI), PTSD - Post-traumatic Stress Disorder, Anhedonia, Predictive Biomarkers, Uncinate Fasciculus

Poster Abstracts

Thursday, May 10, 2018

POSTER SESSION 1
5:00 p.m. - 7:00 p.m.

T1. Prospective Predictors of All-Cause Mortality and Suicide in Late-Life Depression

Hanga Galfalvy[1], Alexandre Dombrovski[2], and Katalin Szanto[3]

[1]Columbia University, [2]University of Pittsburgh, [3]University of Pittsburgh Medical Center

Background: Life expectancy is reduced in mental illness, making it important to understand the behavioral predictors of early mortality. We tested cognitive and decision competence deficits and personality factors previously implicated in suicide as predictors of deaths from any cause, and of suicide.
Methods: Sample consisted of 311 non-demented depressed older adults (age: 65.6 ±9.8; median follow-up 5.4 years): 153 with prior attempts, 71 with suicidal ideation only, 87 non-suicidal depressed, and 90 non-psychiatric controls. Survival analysis examined mortality from any cause, competing risk models predicted the risk of suicide, adjusted for death from other causes, among ideators and attempters.
Results: 9 subjects died of suicide, one died in an accident, 66 died of natural causes. All-cause mortality was higher among suicide attempters than non-psychiatric controls ($p=0.002$; omnibus $p=0.012$). Controlling for age and physical illness burden, predictors of all-cause mortality included cognitive deficits (cognitive control $p=0.002$, MMSE $p<0.001$, global cognition $p=0.012$), poor self-reported ($p=0.003$) and real-life problem-solving ($p=0.007$). Among attempters and ideators, predictors of suicide were male sex ($p=0.012$), widowhood ($p=0.048$), deficits in decision competence and real-life problem-solving (all $p<0.001$), dysfunctional personality: neuroticism, lower extraversion, lack of conscientiousness (all $p<0.001$), and being a maximizer ($p=0.029$).
Conclusions: Not only do cognitive and decision-making deficits increase suicide risk in old age, but they may also constitute behavioral risk factors for death from other causes. While these findings should be taken with caution considering possible residual confounding by undetected physical illness, suboptimal choices with respect to everyday life and healthcare may shorten life expectancy.
Supported By: MH R01MH085651
Keywords: Suicide, Geriatric Depression, Cognitive Deficits, Decision-Making Competence, Mortality

T2. Functional and Structural Connectivity of the Nucleus Accumbens and Amygdala in Geriatric Depression

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Background: Prior studies implicate focal alterations of the amygdala and nucleus accumbens in depression (Hastings et al., 2004; Baumann et al., 1999). However, disruptions in networks of brain regions more likely account for depression pathophysiology (Barch, 2017). Despite the known roles of the accumbens and amygdala in reward processing and emotional response, there are a shortage of depression studies exploring the structural and functional connectivity of these regions, particularly in geriatric samples. This study used connectivity analysis to address this question in geriatric depression.
Methods: Thirty-five depressed (mean age 70±7; 21 females), and thirty-two non-depressed (mean age 68±9; 17 females) subjects received diffusion-weighted and resting state functional MRI scans. The left and right accumbens and amygdala were used as seeds in structural (probabilistic tractography implemented in FSL) and seed-to-voxel functional (CONN toolbox for SPM) connectivity analysis.
Results: Compared to controls, the depressed group showed decreased connectivity of the left nucleus accumbens both in diffusion ($p<0.05$, TFCE corrected) and functional ($q=0.05$, FDR corrected) MRI data. No age by group interaction, or differences between depressed and non-depressed groups were found for right nucleus accumbens or bilateral amygdala connectivity.
Conclusions: The nucleus accumbens forms a central part of the reward system. Our findings suggest disturbances in both the structural pathways and functional connectivity of this region to other brain regions in geriatric depression, particularly in the left hemisphere. These abnormalities could relate to symptoms of anhedonia commonly observed in late life depression, perhaps more so than disturbances in emotional response that rely more closely on amygdala connectivity.
Supported By: Alzheimer's Research and Prevention Foundation; NIH Grants MH097892; MH086481; AT009198; AT008383
Keywords: Geriatric Depression, Connectivity, Nucleus Accumbens, Amygdala

T3. Influence of Study Population Definition on the Effect of Age at Incident Traumatic Brain Injury

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Background: The objective was to determine how study population definition influences the effect of age on TBI recovery. As age is a criterion used to determine whether a blunt head trauma patient receives a head computerized tomography (CT) scan, we hypothesized that when looking at all comers receiving CT after blunt head trauma, fewer older individuals would meet Veterans Administration and Department of Defense (VA/DoD) criteria for TBI, and would, therefore, display better outcomes than younger. However, restricting to participants meeting VA/DoD criteria for TBI, we hypothesized that older individuals would have worse outcomes.
Methods: Data from a recently completed prospective cohort study was used and age was dichotomized at 65 years (<65, n=391; >65, n=109). Logistic regression modeling, controlled for potential confounders and head trauma severity, was used to measure the effect of age on functional recovery, post-concussive (PCS), and depressive symptoms at one-month post-TBI.
Results: Fewer older than younger individuals met VA/DoD criteria for TBI (58% vs. 77%, p<0.001). Looking at all-comers, older individuals had fewer functional (OR=0.26, p<0.001), PCS (OR=0.30, p<0.001), and depressive symptoms (OR=0.42, p=0.005) at one month. Restricting to those meeting VA/DoD criteria for TBI, older individuals continued to have fewer functional (OR=0.24, p<0.001) and PCS (OR=0.33, p=0.003), and were similar to younger in depressive (OR=0.51, p=0.079), symptoms.
Conclusions: Contrary to our hypothesis, study population definition did not have a strong influence on the effect of age on TBI outcome. Surprisingly, there was a tendency towards older adults having better outcomes.
Supported By: ImmunArray, Inc.
Keywords: Traumatic Brain Injury, Aging, Post-Concussive, Depressive Symptoms, Recovery Trajectory

T4. Test-Retest Reliability of an Emotional Faces Task and the Impact of Data Quality

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Background: Tasks involving emotional faces processing are often used in conjunction with functional MRI to probe how amygdala function relates to psychiatric disorders (e.g., anxiety disorders) and associated treatments. The clinical utility of fMRI assessment is reliant on adequate test-retest reliability, but previous findings in this regard have been highly variable. We examined test-retest reliability of amygdala activation during emotional faces processing and how data quality variables affect this reliability.
Methods: In an ongoing study, eighteen healthy adults completed an emotional faces task (matching of emotional faces versus shapes) during fMRI on two separate days (Mean: 22.72 days apart). Intraclass correlation coefficients (ICCs: single-measure/average-measure) were calculated for activation (faces-shapes) extracted from bilateral amygdala spheres (5 mm radius, coordinates identified via neurosynth.org). Spearman correlations were used to examine relationships between amygdala activation changes and data quality changes between scan sessions. Data quality variables included the average Euclidean Norm (ENORM) of motion parameters and the temporal signal-to-noise ratio (tSNR).
Results: Moderate test-retest reliability was identified for the left (ICCs: .30/.47) and right amygdala (ICCs: .47/.64) for faces-shapes, as well as for angry/fearful faces-shapes for the left (ICCs: .36/.53) and right amygdala (ICCs: .32/.48). Left amygdala activation inconsistencies were significantly correlated with inconsistencies in ENORM values ($r = .58$; $p = .01$).
Conclusions: These preliminary findings suggest that amygdala activation during an fMRI emotional faces task has moderate test-retest reliability. Methods for limiting participant motion in order to maximize data quality may be important for optimizing test-retest reliability of fMRI paradigms and supporting clinical utility.
Supported By: NIMH K23MH108707
Keywords: Reliability, Emotional Faces, Amygdala, Anxiety, Data Quality

T5. Brain Before Behavior: Temporal Dynamics in the Treatment of Social Anxiety - Neural Changes Occur Early and Precede Clinical Improvement

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Background: The brain rapidly responds to affective processing and neural responsivity can separate anxiety disorder patients from healthy individuals. Psychiatric treatment also alters brain responsiveness however, the brain's temporal dynamics during treatment remain unknown. Here, patients with social anxiety disorder (SAD) were treated with cognitive-behavioral therapy (CBT) and functional magnetic resonance imaging (fMRI) assessments were performed before, during and after intervention.
Methods: Forty-six SAD patients received a 9-week Internet-delivered CBT and symptoms were assessed weekly using the Liebowitz social anxiety scale (LSAS-SR). MRI was acquired at 4 time-points (2 baselines, mid- and post-treatment). Blood-oxygen level-dependent (BOLD-fMRI) was performed while patients viewed negative facial expressions. BOLD-fMRI data was reviewed manually by classifying signal from noise, all subjects contributing with complete data.
Results: Patients improved slightly from baseline to mid-treatment (P<.001, Cohen's d=0.34) on the LSAS-SR, but more so from mid- to post-treatment (P<.001, d=1.46). Whole-brain neural responsivity decreased from baseline to post-treatment (False Discovery Rate, FDR P<.005) in the medial prefrontal cortex, precuneus and amygdala/parahippocampus. However, no changes (FDR P>.05) from mid- to post-treatment were found, suggesting that the early alterations accounted for the effect. Furthermore, early response

reductions were positively associated with symptom improvement from pre-post treatment (Pearson's r=.50, P<.001).
Conclusions: This is, to our knowledge, the first study assessing early and late psychiatric treatment changes in the brain. Interestingly, altered neural responsivity in limbic and default-mode network regions preceded self-reported alleviation of social anxiety. Understanding the brain's temporal dynamics and subsequent modification of behavior may be highly important for future clinical neuroimaging research.
Keywords: Social Anxiety Disorder, BOLD fMRI, Cognitive Behavior Therapy, Temporal Dynamics, Amygdala

T6. Neural Activations Differentiate Five Subtypes of Anxiety Defined by the SCARED

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Background: The current Diagnostic and Statistical Manual (DSM-5) recognizes multiple unique anxiety disorders. It has been suggested that different anxiety disorders have unique neural underpinnings, though studies investigating this notion are limited, particularly with respect to children and adolescents. The present study investigated whether there were differences in neural activations to looming threat across a spectrum of anxiety disorders in a large cohort of children and adolescents.
Methods: 138 children and adolescents ages 10-to-19 completed the Screen for Child Anxiety Related Disorders-Self-rated (SCARED-S), which assesses five unique types of anxiety disorders: GAD, SAD, panic disorder, school anxiety, and separation anxiety. Participants also performed a looming threat task during an fMRI session.
Results: We found clear evidence for distinct patterns of neural activation between different types of anxiety disorders identified by the SCARED-S. Areas of differential activation included regions critical in self-concept processing and threat circuitry including medial frontal cortex, posterior cingulate cortex, and the amygdala. We also found evidence for overlapping activation across disorders.
Conclusions: The findings suggest that children and adolescents with different anxiety disorders do exhibit differential neural activation patterns in response to looming threat. Given these data, it is important for clinicians to consider the specificity of interventions for individuals presenting with different types of anxiety disorders. By catering treatment regimens to target maladaptive neural systems activations that are unique to a disorder group, in addition to those systems activations that are shared across anxiety disorders, clinicians may be able to better address and alleviate clients' symptoms.

Supported By: Boys Town National Research Hospital, National Institute of All Mental Health
Keywords: Anxiety Disorders, Brain Imaging, fMRI, Children and Adolescence

T7. Habitual Use of Reappraisal and Psychophysiological Reactivity to Unpredictable Threat: An Event-Related Potential and Startle Eyeblink Study

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Background: Cognitive reappraisal is an emotion regulation strategy that is associated with psychiatric health and well-being, whereas reduced use of this strategy and increased reliance on less effective strategies may characterize affective psychopathologies such as anxiety and depression. Prior work has shown that less habitual use of reappraisal is associated with increased amygdala and reduced prefrontal and parietal brain activity to negative stimuli (e.g., faces). Here, we inquired whether individuals who reported less everyday use of reappraisal would exhibit increased event-related potentials (ERPs) and fear-potentiated startle during unpredictable threat - a construct of particular relevance to anxiety.
Methods: 78 unselected adults (32 males, 46 females) performed a version of the No Shock, Predictable Shock, Unpredictable Shock (NPU) task. Cue-locked P300 and late positive potential (LPP) ERP amplitudes as well as startle eyeblink were used to assess processing of predictable and unpredictable threat. Participants completed the Emotional Regulation Questionnaire (ERQ) to assess their habitual use of cognitive reappraisal and expressive suppression.
Results: Participants who reported less habitual use of reappraisal showed larger P300s, $r(71) = .424$, $p < .001$, LPPs, $r(71) = .277$, $p = .017$ and startle amplitudes, $r(71) = .281$, $p = .019$ for unpredictable compared to no-shock trials. No significant associations were found involving predictable threat or ERQ suppression scores (all ps > .1).
Conclusions: Less habitual use of reappraisal is associated with increased reactivity to unpredictable threat across multiple measures. Interventions aimed at increasing everyday use of reappraisal might help mitigate this putative risk factor for anxiety.
Supported By: National Institute of Mental Health K23 MH105553
Keywords: Reappraisal, Emotion Regulation, Startle, Late Positive Potential, Anxiety

T8. An Abrupt Transformation of Spider Phobic Behavior After a Post-Retrieval Amnesic Agent

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Background: Although disrupting the process of memory reconsolidation has a great potential for clinical practice, the fear-amnesic effects are typically demonstrated through Pavlovian conditioning. Given that older and stronger memories are generally more resistant to change, we tested

whether disrupting reconsolidation would also diminish fear in individuals who had developed a persistent spider fear outside the laboratory.
Methods: Spider-fearful participants received a single dose of 40 mg of the noradrenergic β-blocker propranolol (n = 15), double-blind and placebo-controlled (n = 15), after a short 2-min exposure to a tarantula. To test whether memory reactivation was necessary to observe a fear-reducing effect, one additional group of spider-fearful participants (n = 15) received a single dose of 40 mg propranolol without memory reactivation.
Results: Disrupting reconsolidation of fear memory transformed avoidance behavior into approach behavior in a virtual binary fashion — an effect that persisted at least 1 year after treatment. Interestingly, the β-adrenergic drug did initially not affect the self-declared fear of spiders but instead these reports followed the instant behavioral transformation several months later.
Conclusions: Our findings are in sharp contrast with the currently pharmacological and cognitive behavioral treatments for anxiety and related disorders. The β-adrenergic blocker was only effective when the drug was administered upon memory reactivation, and a modification in cognitive representations was not necessary to observe a change in fear behavior. A new wave of treatments that pharmacologically target the synaptic plasticity underlying learning and memory seems to be within reach.
Supported By: NWO-VICI
Keywords: Anxiety Disorders, Fear Memory, Propranolol, Reconsolidation, Spider Phobia

T9. Intrinsic Functional Connectivity of the BNST vs. CeA Using 7T fMRI in Experimentally-Induced Anxiety and Pathological Anxiety

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Background: Defensive responses are of two types: fear, acute response to imminent threat; and anxiety, sustained response to uncertain threat. Within the extended amygdala, a dissociation has been proposed for the involvement of the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST): the CeA preferentially in fear, and the BNST in anxiety. However, this dissociation remains debated. Using ultra-high field MRI, we initiated a series of studies to clarify the respective functional position of the CeA and BNST across the brain in anxiety.
Methods: Whole-brain intrinsic functional connectivity (iFC) for CeA and BNST seeds was assessed on 7Tesla scans from three studies: (1) 10-min rest (n=27 healthy), (2) 16-min rest & sustained threat of electrical shock (n=36 healthy), and (3) 10-min rest in anxious patients (n=30 patients, n=30 healthy) (All results whole-brain corrected at $p<0.05$).
Results: Across the three studies: (1) At rest, CeA-iFC vs. BNST-iFC was stronger with regions involved in somatosensory processing (eg insula, thalamus, fusiform); BNST-iFC vs. CeA-iFC was stronger with regions processing cognition (eg caudate, medial-PFC); (2) Sustained threat vs. safety mainly reduced BNST-iFC and CeA-iFC; (4) patients vs. healthy showed reduced iFC of selected regions coupled with the BNST and the CeA.
Conclusions: Consistent with fear, CeA privileges coupling with somatosensory regions, and, consistent with anxiety, BNST privileges coupling with cognitive regions. Sustained threat and clinical anxiety might dynamically modulate iFC, or involve intermediary networks, resulting in reduced coupling. Most of these data are not yet published.
Supported By: NIMH-Intramural, ZIAMH002798
Keywords: Anxiety, Ultra-High Field 7-Tesla MRI, Extended Amygdala (CeA/BST), Threat Response

T10. Effects of PACAP Receptor Gene Polymorphism on Limbic-Based Brain Functional Organization in Youth

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Background: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a protein involved in the neurophysiological stress response. A single nucleotide polymorphism (SNP; rs2267735) in the gene encoding the PAC AP receptor, PAC1, has been linked to risk of posttraumatic stress disorder and reduced functional connectivity of limbic brain areas associated with stress-related processing, including the amygdala and the hippocampus in adults. Although stress-related psychopathology frequently begins during childhood and adolescence, no studies have examined the potential link between PACAP receptor genotype and limbic-based functional brain organization in youth.
Methods: Forty-five youth, ages 6-17 (26 females), participated in this preliminary imaging genetic study. DNA was extracted from saliva samples, and Taqman Genotyping was performed for the PACAP receptor SNP rs2267735. Participants also completed a 10-minute resting-state functional magnetic resonance imaging (fMRI) scan and functional connectivity between the amygdala and hippocampus was compared between CC and G-allele carriers. Graph theory measures were calculated to characterize the topological properties (i.e., limbic regional nodal parameters) between genotype.
Results: There was no effect of genotype on resting-state functional connectivity between the amygdala and hippocampus, however youth with the CC genotype (n=11) demonstrated lower local efficiency of the right hippocampus (p=0.046), compared to G-allele carriers (n=34). There were no effects of genotype on local efficiency of the amygdala, or other tested network properties (i.e., betweenness centrality, degree, clustering coefficient).
Conclusions: Reduced local efficiency of the hippocampus may reflect altered information processing, and suggests that PACAP receptor genotype influences limbic-based brain organization earlier in life than previously demonstrated.
Supported By: American Cancer Society Institutional Research Grant; WSU Department of Pharmacy Practice
Keywords: Polymorphism, Youth, Hippocampus

T11. Contributions of Cortico-Striatal Pathways to the Modulation of Cognitive Flexibility

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Background: Cortico-striatal circuits are central to several cognitive processes, including decision-making, inhibitory response control, and attentional set-shifting. Deficits in these processes are common in obsessive-compulsive disorder (OCD), major depression (MDD), and many other disorders. Considering that deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is effective in reducing the symptoms of refractory OCD and MDD, we hypothesize that DBS may act by improving executive processes that lead to increased cognitive flexibility.
Methods: We investigated how DBS-like electrical stimulation of the VC/VS in rodents affects cognitive flexibility in an operant set-shifting paradigm. DBS (0 − 300 μA) was delivered to the VCVS for 1 h prior to the set-shifting test. Additionally, animals treated with meta-Chlorophenylpiperazine (mCPP 2.0 mg/kg) - as an OCD animal model − received similar DBS intervention.
Results: DBS (300 μA) significantly improved animals' reaction times (RT, -22 ms mean difference, t=-2.27, p=0.02 for regression coefficient, n=6). In the second part of the study, DBS reduced RT (-31 ms, t=-2.44, p=0.01), while treatment with mCPP and drug treatment combined with DBS increased RT (+310 ms, t=19.05, $p<0.01$; +127 ms, t=5.19, $p<0.01$).
Conclusions: Our data suggest that DBS may affect PFC functioning in ways that improve flexibility. This might occur by modulation of striatum/thalamus through efferent cortico-striatal projections, or by antidromically activating those same fibers and directly modulating PFC. mCPP impairments could be explained in terms of the altered serotonergic/dopaminergic modulation of PFC neuronal activity. Further experiments will clarify which PFC sites are most involved in the DBS modulation of cognitive flexibility.
Supported By: This work is supported by the Brain & Behavior Research Foundation, the Harvard Brain Initiative Bipolar Disorder Fund and a private donation from Dr. Michael Jenike
Keywords: Cortico-Striatal-Thalamic-Cortical Circuit, DBS, Cognitive Flexibility, Obsessive Compulsive Disorder (OCD)

T12. Prefrontal Regulatory Pathways in Young Non-Human Primates That Modulate the Function of the Neural Circuitry Underlying Anxious Temperament

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Background: Our previous work demonstrated the importance of prefrontal regulation on mediating the early-life risk to develop anxiety and depression. To examine the role of prefrontal regulation on subcortical structures in mediating anxious temperament (AT), we assessed the effects of aspiration lesions of a narrow strip of cortex in posterior area 13 and medially in area 14/25, which also disrupted fibers of passage and adjacent white matter.
Methods: Ten young female lesioned monkeys and 10 controls were behaviorally tested and underwent MRI, DTI, and FDG-PET scans. In a separate sample, tracing studies were performed to better characterize pathways coursing through the lesioned region.
Results: Significant reductions in fractional anisotropy (FA) occurred in the uncinate fasciculus along with reductions in metabolism in the anterior cingulate cortex (ACC), bed nucleus of the stria terminalis (BST) and midline thalamus. We used the affected BST region, which in a larger sample predicted AT, as a seed to explore alterations in resting-state functional connectivity. The lesions induced disruptions in connectivity between this seed and the ACC (area 24/32) and ventrolateral prefrontal cortex (area 45, $p<.005$, uncorrected). Tract tracing studies identified pathways connecting the ACC with BST and midline thalamus, suggesting the possibility that the most medial aspects of the lesion could account for some of the observed changes.
Conclusions: Damage to OFC and adjacent white matter connecting PFC to subcortical structures results in decreased BST metabolism and altered PFC-BST connectivity. These data suggest that the PFC plays an important role in modulating BST function in relation to anxiety.
Supported By: MH046729, MH081884, MH084051
Keywords: Anxiety, Non Human Primate, Orbital Frontal Cortex, Lesion, Bed Nucleus of the Stria Terminalis

T13. D-Cycloserine Facilitates Fear Extinction in Adolescent Rats and Differentially Affects Medial and Lateral Prefrontal Cortex Activation

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Background: Adolescents, both humans and rodents, exhibit a marked impairment in extinction of learned fear relative to both younger (i.e., juveniles) and older (i.e., adults) groups. This impairment could be due to the medial or lateral prefrontal cortex (PFC) not being efficiently recruited during extinction. For example, unlike juveniles and adults, adolescent rats do not express extinction-induced increases in phosphorylated mitogen activated protein kinase (pMAPK), a marker of synaptic plasticity, in the medial PFC. The NMDA receptor partial agonist D-cycloserine (DCS), which enhances exposure therapy in humans with anxiety disorders, overcomes the extinction retention deficit in adolescent rats. The present experiments investigated the effects of DCS on the PFC and amygdala by measuring pMAPK-immunoreactive (IR) neurons.
Methods: Male adolescent rats were trained to fear a white-noise conditioned stimulus in one context followed by extinction in a second context or equivalent context exposure only (i.e., no extinction). DCS (15 mg/kg, s.c.) or saline was administered systemically immediately after extinction training or the context exposure.

Results: The findings suggest that DCS enhances extinction retention in adolescent rats primarily by increasing activation of the MAPK signalling pathway in the lateral PFC within the orbitalfrontal cortex after extinction training (p = .010). However, when rats were tested for extinction retention, DCS-injected adolescents had fewer pMAPK-IR neurons in the orbitalfrontal cortex (p=.04) but more pMAPK-IR neurons in the medial PFC (p=.025) than saline-injected adolescents (ns=9-10).
Conclusions: The present findings provide insight into the neural mechanisms underlying a pharmacological approach for improving fear inhibition in a vulnerable age group.
Supported By: ARC grant DP110100754; NHMRC grants APP1086855 and APP1054642.
Keywords: Fear Extinction, Adolescence, Prefrontal Cortex, Amygdala, D-Cycloserine

T14. Individual Differences in Extinction and Relapse: Who, Why, and What Can We Do?

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Background: We have recently demonstrated that vulnerability to relapse of fear is related to individual differences in the rate of extinction (with slow extinguishers being more vulnerable). Here we examined the molecular basis for these individual differences in rate of extinction and found differences between "fast" and "slow" extinguishers in NMDA receptor protein levels. We then examined whether this translated to differences in responding to an NMDA receptor partial-agonist, D-cycloserine (DCS).
Methods: On consecutive days rats were conditioned to fear a white-noise CS, received extinction to a criterion, and were tested for extinction retention. The number of blocks to reach the criterion was used to classify animals as "fast" or "slow" extinguishers. Animals were euthanased and the amount of NR1, NR2A and NR2B protein in the PFC, amygdala, and hippocampus was analysed by Western Blotting. In a second series of experiments we examined the effects of a post-extinction injection of DCS on relapse.
Results: Averaging across brain regions, we found that fast extinguishers had more NR1 protein and less NR2A and NR2B protein than did slow extinguishers. We also found that DCS reduced relapse for fast extinguishers but had minimal effects for slow extinguishers.
Conclusions: Here we identified NMDA receptors as a potential biomarker involved in individual differences in rate of extinction. These findings contribute to a growing literature identifying factors that influence the efficacy of pharmacological adjuncts and might provide insight into how to enhance resilience.
Supported By: NHMRC; ARC
Keywords: D-Cycloserine, Fear Extinction, Individual Differences, Relapse

T15. Paired, Phase-Lagged Electrical Stimulation Alters Connectivity and Plasticity in a Fear Regulation Circuit

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Background: Brain connectivity may depend on the oscillatory synchrony of local field potential (LFP) between regions. For instance, synchronized low-frequency oscillations in fronto-amygdalar circuits are strongly implicated in fear regulation. Clinical exploitation of this knowledge is limited by the lack of established methods for manipulating oscillatory synchrony. We describe a brain stimulation technique to alter oscillatory synchrony in a rodent model.
Methods: 6 Hz pulse trains were delivered to the infralimbic cortex (IL) and the basolateral amygdala (BLA) of Long-Evans rats (n=5), with variable phase lags between pulses (0° and 180°). We measured entrainment of the low-frequency LFP (coherence) and connectivity changes (single-pulse evoked potential response to/from IL and BLA) before and every 15 minutes from 0 to 90 minutes after the stimulation.
Results: Paired electrical stimulation with a 180° lag between IL and BLA increased coherence by 3 standard deviations over baseline. The evoked potential increased 3.5 times (p=1.8×10-40) in the IL->BLA direction and decreased 20% (p=0.0069) in the BLA->IL direction. The connectivity changes lasted for at least 90 minutes after stimulation. Thus, stimulation enhanced a top-down connection from IL to BLA while suppressing the bottom-up connection from BLA to IL.
Conclusions: Brain stimulation technique that alters oscillatory synchrony and connectivity may provide a new technique to study brain networks, and may serve as a basis for new treatments for neuro-psychiatric disorders. We intend to apply this to alter anxiety-related behaviors, probing the role of oscillations in this circuit.
Supported By: NIH R21
Keywords: Deep Brain Stimulation, Electrophysiology, Corticolimbic, Neural Oscillations, Fear and Anxiety

T16. Discovery of Novel Blood Biomarkers for PTSD and TBI

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Background: The development of blood biomarkers for PTSD and TBI is an extremely critical area of research. Easily detectable blood biomarkers are needed for diagnostic purposes, to establish therapeutic efficacy, to better understand the biology underlying these disorders.
Methods: We analyzed biologically-driven blood biomarkers in a Cohort of Iraq and Afghanistan combat veterans and civilians recruited at the NYU Cohen Veteran Center. All subjects underwent fasting blood draws. Blood was processed following best practices for biomarkers analysis. Specific biomarkers assays were performed using Simoa or ELISA platforms.
Results: Blood Biomarkers were tested in PTSD, chronic TBI, PTSD + chronic TBI and control subjects. Proteins, peptides and hormones chosen as candidate biomarkers were part of pathways involved in cerebral and metabolic stress and

neurodegeneration, altered in PTSD and/or TBI patients. These pathways included inflammation, stress response/HPA axis, neurotrophic factors and neuropathology indicators released in acute TBI, such as tau. Comorbidity with depression and alcohol use were considered. Results differed depending on the biological target, and were statistically significant for multiple markers analyzed, with $p<0.001$ to separate PTSD from Control and TBI patients in groups of at least 60 subjects for our best hit target. Novel potential biomarkers for PTSD were identified, reaching AUC 0.75 to separate Controls from PTSD and 0.82 to separate PTSD from TBI with a single molecule.
Conclusions: As no biofluid biomarkers for PTSD or chronic TBI are currently available, this work paves the way to the development of blood tests for diagnosis, treatment and biological understanding of these disorders.
Supported By: NIH, Cohen Veterans Bioscience, Leon Levy Fellowship
Keywords: Biomarkers, PTSD, TBI, Blood

T17. The Role of mPFC in Escape From an Innate Fear Stimulus

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Background: In rodents, specialized visual circuits gate escape behavior from a looming stimulus, which is thought to be similar to predator attack. However, recent work has demonstrated that mice rely on a pre-learned safe location that they then use during the escape. The mPFC receives projections from the hippocampus and has previously been shown to contain neurons representing distance from emotionally salient stimuli.
Methods: We inactivated the mPFC of adult male mice (muscimol), then assessed the response to looming stimulus. In a separate cohort, we performed in vivo calcium imaging in the prelimbic prefrontal cortex of behaving animals as they explored and then responded to the looming stimulus.
Results: Inactivation of mPFC prevented escape from the looming stimulus ($n=8$, crossover design, $p<0.05$). Results from in vivo imaging experiments demonstrate the existence of individual neurons correlating with distance from a safe hiding place in the mPFC ($n=99$ neurons).
Conclusions: Together, these results suggest that mPFC is necessary for escape from an innate fear stimulus. Neurons representing distance from safety could be a potential mechanism by which mPFC integrates spatial and emotional information. Innate defensive responses depend upon top-down modulation by mPFC, and merit further study in translational models of psychiatric disorders.
Supported By: National Institute of Mental Health grant R01MH112750 (A.C.K.), National Institute of Mental Health grant R21MH110712 (A.C.K.), NARSAD Young Investigator Award (A.C.K.), and Inscopix DECODE award (A.C.K.), T32MH019961 (APK), T32MH014276 (APK), R25MH071584 (APK), Thomas P Detre Fellowship (APK)
Keywords: Predator Threat, mPFC, PTSD - Posttraumatic Stress Disorder, Anxiety, Safety

T18. Characterizing Reward Responsiveness in Obsessive-Compulsive Disorder and Schizophrenia Through a Probabilistic Reward Task

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Background: Deficits in reward processing occur across the psychiatric spectrum. Identifying common and distinct impairments in the maintenance and integration of reward information may lead to a greater understanding of the mechanisms behind the affective disturbances across schizophrenia (SCZ) and obsessive-compulsive disorder (OCD). Here, we used the probabilistic reward task (PRT) to test the ability to learn implicit reward reinforcement across patients diagnosed with SCZ and OCD.
Methods: Reward responsiveness was assessed in SCZ patients ($N=15$) relative to OCD patients ($N=11$) with similar levels of self-reported depression and a demographically-matched control group ($N=20$). PRT consisted of two stimuli, one of which was rewarded more frequently. Response bias was defined as a participant's tendency to favor the more frequently rewarded stimulus as a function of previous reward feedback. Responsive bias, as well as its constituent components (favored and non-favored stimulus hits and misses), were calculated across three trial blocks.
Results: Relative to SCZ and controls, OCD patients demonstrated reduced change in response bias between the first and final blocks. This was driven by response bias during the first trial block being significantly higher for OCD than SCZ and controls. While response bias for SCZ and controls increased across blocks, it remained the same for OCD patients.
Conclusions: These results indicate that SCZ and OCD exhibit distinct abnormalities in their ability to acquire implicit reward reinforcement, despite similar levels of mood symptomatology. These cross-diagnostic effects points to putative differences in neural mechanisms that may drive affective dysfunction cross-diagnostically.
Supported By: BlackThorn Therapeutics
Keywords: Schizophrenia, Obsessive Compulsive Disorder (OCD), Probabilistic Reward, Affective Dysfunction

T19. Sleep Problems are Associated With Greater Default Mode Network Activation When Anticipating Negative Stimuli in Individuals With PTSD

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[1]University of Arizona

Background: Sleep difficulties represent some of the most common complaints of individuals with post-traumatic stress disorder (PTSD). Sleep problems can affect daytime alertness and can lead to many functional impairments. The extent to

which these impairments are associated with altered brain functioning in PTSD is not currently known. Here, we correlated daily sleep related impairments with functional brain responses when anticipating an aversive visual image.
Methods: Thirty-one adults (14 male; 17 female, mean age=30.6) meeting diagnostic criteria for PTSD underwent functional magnetic resonance imaging while completing an emotional anticipation task. Participants were given cues to anticipate either a positive or negative visual image that subsequently appeared on the screen. They also rated the impact of excessive sleepiness on daily activities and quality of life using the Functional Outcomes of Sleep Questionnaire (FOSQ).
Results: During anticipation of negative stimuli (in contrast to no anticipation), greater FOSQ sleep impairments correlated positively with activation within the medial prefrontal cortex [x=-4, y=40, z=-12]; k=317; p=<0.001, FWE cluster-corrected] and the posterior cingulate/retrosplenial cortex [x=-8, y=-46, z=38]; k= 82; p< 0.001, FWE cluster-corrected], two key midline structures of the default mode network (DMN).
Conclusions: Among patients with PTSD, greater sleepiness-related impairments were associated with increased activation of the medial DMN when anticipating negative but not positive visual stimuli. Because the DMN is activated during self-referential processing, this suggests that excessive sleepiness and sleep-related impairments may exacerbate the tendency to associate negative cognitions with self-processing. Addressing sleep problems may be important for recovery in PTSD.
Supported By: Department of Defense - USAMRMC
Keywords: PTSD, Sleep Disturbances, Emotional Anticipation, Default Mode Network

T20. Improvements in PTSD Symptom Severity are Associated With Greater Activation in the Hippocampus During Anticipation of Negative Stimuli

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[1]University of Arizona

Background: Post-Traumatic Stress Disorder (PTSD) is often associated with distorted emotional contextualization of memories, leading to re-experiencing symptoms and flashbacks in novel situations. The hippocampus is integrally involved in both memory and emotional regulation. Individuals with PTSD often have reduced hippocampal activity during memory-related tasks. Here, we investigated whether time-dependent improvement in PTSD symptom severity correlated with changes in hippocampal activity during an emotional anticipation task.
Methods: Twenty-eight individuals with PTSD (Female=13, mean age=318.2) were randomized to receive blue (n=14) or placebo amber (n=14) light therapy (30-mins/morning for 6 weeks). The Clinician-Administered PTSD Scale (CAPS) and an emotional anticipation task during fMRI were administered at pre- and post-treatment visits. Changes in functional brain activation when anticipating negative stimuli in contrast to a no-anticipation baseline condition were analyzed. We correlated these functional activation changes with post-treatment CAPS score changes.
Results: CAPS scores improved between visits (mean change pre-post=-4.12.97), however, there were no significant differences between the blue and amber groups. Whole brain analyses showed that lower post-treatment CAPS scores were associated with increased hippocampal activity during negative anticipation (x=-34, y=-32, z=-18, k=39, p<.005, uncorrected).
Conclusions: Previous studies demonstrate that individuals with PTSD often have reduced hippocampal activation during memory tasks, with corresponding deficits in context-relevant emotional responses. Our preliminary results suggest improvement in PTSD symptom severity over time may lead to increased hippocampal activation when anticipating negative stimuli. This change in hippocampal activation may be important for encoding new contextual information about negative stimuli that may have previously triggered re-experiencing symptoms.
Supported By: Department of Defense-USAMRMC
Keywords: PTSD - Posttraumatic Stress Disorder, Hippocampus, Emotional Memory, Anticipation

T21. Daytime Sleepiness in Individuals With PTSD is Associated With Greater Activation in the Right Angular Gyrus When Viewing Negative Images

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[1]University of Arizona

Background: Post-traumatic stress disorder (PTSD) is often associated with poor sleep quality that can result in increased daytime sleepiness. However, it is unknown how increased daytime sleepiness may affect functional brain responses during emotion processing. We hypothesized that greater daytime sleepiness in individuals with PTSD would lead to increased hypervigilant brain activation responses within the attentional system when viewing negative versus positive images during functional magnetic resonance imaging (fMRI).
Methods: Thirty-one individuals clinically diagnosed with PTSD (Nfemale=17; Mage=30.66, SDage=8.39) completed the Epworth Sleepiness Scale (ESS), a measure of daytime sleepiness, as well as an emotional anticipation task during fMRI. The task included exposure to highly pleasant and unpleasant images from the International Affective Picture System.
Results: For unpleasant versus pleasant images, whole brain analyses showed a significant positive association between ESS scores and activation within a cluster spanning the middle occipital lobe and the right angular gyrus (x=46, y=-64, z=26; k=125, p=.005, FWE-cluster corrected).
Conclusions: Greater daytime sleepiness was associated with greater activation in the right occipital-parietal cortex when viewing negative versus positive images. Considering the role of the angular gyrus and inferior parietal regions in shifting attention to salient stimuli, our findings suggest that daytime sleepiness may reduce cognitive control, leading to increased attention toward negative stimuli. Behaviorally, this may be reflected in a greater negative attentional bias, contributing to the maintenance of PTSD. Interventions focused on improving sleep quality may prove useful for minimizing the tendency toward negative attentional biases in individuals with PTSD.

Supported By: Department of Defense - USAMRMC
Keywords: PTSD - Posttraumatic Stress Disorder, Daytime Sleepiness, Negativity Bias, Brain Imaging, fMRI

T22. PTSD Symptom Profiles and Amygdala Function Vary as a Function of Repeated Trauma Exposure: Numbing as a Specific Neurobiological Phenotype

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Background: In posttraumatic stress disorder (PTSD), individuals with a history of multiple traumas show blunted sympathetic nervous system responses relative to those with a single trauma. We characterized trauma exposure history in a large-cohort study of PTSD, and examined effects of trauma chronicity and severity on symptom patterns and brain function.
Methods: N=6271 participants reported on lifetime trauma histories and current symptoms. Trauma history was quantified using number of types of traumas in childhood and adulthood, quantity and severity of childhood abuse, age of first exposure, and time since most recent trauma. Amygdala function was examined in a sub-sample (N=100) who viewed fearful and neutral face stimuli during fMRI.
Results: Multivariate PTSD symptom patterns changed with the number of childhood abuse exposures, $F(8,12402)=125.8$, $p=1.3 \times 10\text{-}203$. More childhood abuse predicted a greater numbing to re-experiencing ratio; each additional exposure predicted an M=58% increase in numbing. Multiple childhood abuse exposures also predicted greater amygdala habituation to fearful face stimuli, $F(2,96)=5.7$, $p=.005$. Amygdala habituation mediated the relationship between abuse and numbing symptoms.
Conclusions: Numbing symptoms are more likely after repeated exposure to trauma, particularly childhood abuse. This may be related to a pattern of disengagement or blunting of the brain's emotional responses to threat. Longitudinal research is needed to directly test whether the prototypical presentation of PTSD involving primarily re-experiencing and hyper-arousal symptoms converts to a more treatment-resistant form of PTSD characterized by numbing. Further research on the brain processes underlying such changes will reveal new targets for intervention in treatment-resistant PTSD.
Supported By: R01 MH071537; R21 MH098212
Keywords: PTSD - Posttraumatic Stress Disorder, Anhedonia, Childhood Trauma, Trauma Exposure, Chronic Stress

T23. Resting State Functional Neural Network Modularity Among Adult Women With PTSD

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Background: A wealth of neuroimaging data focuses on models of posttraumatic stress disorder (PTSD) that implicates bi-nodal functional connectivity (BNFC) between the amygdala and medial prefrontal cortex. As neuroimaging research advances toward evaluating psychopathology in the context of neural organization into large-scale network models, how to integrate findings based on BNFC models remains unclear. Modularity is one metric by which network organization can be quantified. Prior research on interpersonal trauma (IT) among adolescent girls suggests that altered BNFC generally reflects large-scale network modularity patterns, however, this finding requires replication in larger samples of adults.
Methods: The present study examined resting-state activity during 3T fMRI with 12 healthy control women and 65 women with a history of direct physical and/or sexual assault exposure and a current PTSD diagnosis. Node-based graph theory analyses focused on large-scale functional network organization using a 204 regions-of-interest atlas.
Results: Both physical and sexual abuse exposure were associated with greater large-scale network modularity, $r(77)=.32$, $p<.05$. Across all networks, both physical and sexual abuse exposure were associated with weaker overall between-module connectivity, $r(60)=.29$, $p<.03$; $r(62)=.31$, $p<.02$, whereas only sexual abuse was associated with weaker overall within-module connectivity, $r(60)=.32$, $p=.02$, $r(62)=.22$, $p=.63$.
Conclusions: Consistent with findings on adolescent girls with IT exposure, the current study suggests higher overall network modularity and weaker between-module connectivity among adult women with IT exposure. The study characterized large-scale network patterns specific to trauma type, though future studies might examine the potential causal relationship between network organization and PTSD symptom presentation following IT.
Supported By: NIMH
Keywords: PTSD, Resting State fMRI, Functional Connectivity, Network Analysis, Trauma Exposure

T24. The Behavioral and Neural Correlates of Memory Suppression in PTSD

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Background: Previous work has shown that healthy individuals can actively suppress emotional memories through recruitment of the lateral prefrontal cortex. By contrast, individuals with posttraumatic stress disorder (PTSD) have difficulty suppressing negative information, giving rise to symptoms such as intrusive thoughts. However, little is known regarding the behavioral and neural effects of memory suppression in PTSD.
Methods: In this study, we examined memory suppression in PTSD using the Think-No-Think paradigm in an event-related fMRI study. We studied three groups: PTSD (n=16), trauma-exposure without PTSD (n=19), and healthy controls (n=13). The White Bear Suppression Inventory (WBSI) was also administered as a measure of trait suppression.
Results: There was a main effect of behavioral performance such that memories in the "think" condition were better remembered that memories in the "no-think" condition ($p<0.04$). Further, more healthy controls were classified as

memory suppressors than the trauma-exposed or PTSD groups (all p's<0.05). Neuroimaging data revealed that relative to the trauma-exposed and PTSD groups, the healthy control group also displayed greater activation in the lateral prefrontal cortex during memory suppression. Additionally, the WBSI was negatively correlated with this brain region in both trauma exposed and PTSD groups, but not in controls.

Conclusions: These results suggest that trauma exposure even in the absence of PTSD is associated with disruptions in memory suppression and that reduced activation in the lateral prefrontal cortex may be a potential vulnerability factor for disruptions in both state and trait suppression after trauma exposure.

Supported By: NIMH training grant T32MH019836-01; National Institutes of Health (NIH) grant K23MH084013

Keywords: Emotional Suppression, Emotional Memory, Trauma Exposure, PTSD - Posttraumatic Stress Disorder

T25. Genome-Wide MicroRNA Expression Analysis of PTSD With Comorbid Depression: A Meta-Analysis of Civilian and Veteran Datasets

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Background: microRNAs (miRNAs) are important post-transcriptional regulators of gene expression. Here, we investigated effects of miRNAs on PTSD with comorbid depression.

Methods: PTSD and depression were assessed with the PTSD Symptoms Scale and Beck Depression Inventory. SmallRNA was extracted from whole blood of civilian participants (Grady Trauma Project) and veteran volunteers (Atlanta VAMC) and sequenced on the Illumina HiSeq3000. Global miRNA differential analysis of PTSD with comorbid depression (PTSD/Depression) was performed in the civilian and veteran dataset independently using DESeq2, followed by a meta-analysis.

Results: No miRNA was differentially expressed in PTSD/Depression at FDR p<0.05 in either the civilian (N=66, 767 miRNAs) or veteran dataset (N=71, 786 miRNAs) after adjusting for relevant confounding factors. Among 697 miRNAs profiled in both datasets, we found 335 miRNAs expressed in consistent direction in both datasets and included them in the meta-analysis. The meta-analysis yielded many miRNAs differentially expressed in PTSD/Depression at FDR p<0.05 after adjusting for sex, age, alcohol use, drug use, population substructure, and batch. The top differentially expressed miRNA was miR-1299 (p=0.00045, FDR p=0.0168, N=137).

Conclusions: TargetScan identifies the top target of miR-1299 to be the circular RNA CDR1as. Given our finding of increased miR-1299 level in PTSD/Depression, and given that miRNAs repress expression of their target genes, we hypothesize that blood CDR1as level is downregulated in PTSD/Dep. Notably, deficiency of brain CDR1as was recently found to lead to features associated with neuropsychiatric disorders. We will follow-up these exciting data with further biological replication, integrative mRNA:miRNA analysis, and functional studies of miR-1299 and CDR1as.

Supported By: IK2CX000601; R01AG056533; U01HG009807; MH071537; MH096764

Keywords: microRNAs, Circular RNA, PTSD, Depression, Genome-Wide miRNA Expression Analysis

T26. Transcriptome Analysis Reveals Novel Genes and Networks Dysregulated in Veterans With PTSD

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Background: Posttraumatic stress disorder (PTSD) is a serious condition that emerges following trauma exposure and involves long-lasting psychological suffering and health-issues. Uncovering critical genes and molecular networks is essential to understanding the biology of the disorder. We performed a genome-wide scan to identify novel transcriptome signatures of PTSD.

Methods: Genome-wide peripheral blood transcriptomic data from 380 service personnel were investigated. This included a discovery sample of 96 Australian Vietnam War veterans and two independent pre and post-deployment replication samples of U.S. Marines (N=188 and N=96). Genome-wide gene expression was performed from peripheral blood using the Illumina HT12 arrays. Data analysis was performed using generalized linear regression models, corrected for confounds in R.

Results: 60 transcripts were differentially expressed between veterans with and without PTSD, surviving Bonferroni correction. Genes within the cytokine-cytokine receptor interaction, Jak-STAT signaling and Toll-like receptor signaling pathways were enriched. 49% of gene expression changes were also accompanied by DNA methylation changes. Using two replication U.S. Marine cohort's data, we observed that of the differentially expressed genes, 71% genes also showed significant gene expression changes between pre and post-deployment. Weighted gene co-expression networks revealed two modules of genes associated with PTSD. The first module (67 genes, p-value = 6e-4) was enriched for genes within the 11p13 locus including BDNF. The second module (266 genes, p-value = 0.01) was enriched for genes in 17q11 including SLC6A4, STAT5A and STAT5B.

Conclusions: We identified novel transcriptomic loci and biological pathways and our findings highlight the role of transcriptional biomarkers in the molecular etiology of PTSD.

Supported By: Returned Services League (RSL) Queensland; Gallipolli Medical Research Foundation

Keywords: PTSD - Posttraumatic Stress Disorder, Genome-Wide Gene Expression, Gene Co-Expression Network, War Veterans, Biomarkers

T27. Segregated Cortico-Cerebellar Circuits Revealed by Intrinsic Functional Connectivity in Patients With Obsessive-Compulsive Disorder

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Background: There is growing evidence from resting-state functional connectivity studies reported the segregated cerebral-cerebellar loops may mediate executive, affective, default-mode, and sensorimotor function. Meanwhile, the role of the cerebellum in obsessive-compulsive disorder (OCD) also has drawn increasing attention. However, the functional connectivity between the cerebellum and the cerebral cortex has not been investigated in OCD, nor has the relationship between such functional connectivity and clinical symptoms.
Methods: 27 patients with OCD and 21 healthy controls (HCs) matched on age, gender and education underwent magnetic resonance imaging (MRI). Seed-based connectivity analyses were performed to examine differences in cerebellar-cerebral connectivity in patients with OCD compared to HCs. Associations between functional connectivity and clinical features in OCD were analyzed.
Results: Compared to HCs, OCD patients showed significantly decreased cerebellar-cerebral functional connectivity in executive control and emotion processing networks. Within the OCD group, decreased functional connectivity in an executive network spanning the right cerebellar Crus I and the inferior parietal lobule was positively correlated with symptom severity, and decreased connectivity in an emotion processing network spanning the left cerebellar lobule VI and the lingual gyrus was negatively correlated with illness duration.
Conclusions: Altered functional connectivity between the cerebellum and cerebral networks involved in cognitive-affective processing in patients with OCD provides further evidence for the involvement of the cerebellum in the pathophysiology of OCD, and is consistent with impairment in executive control and emotion regulation in this condition.
Supported By: NSFC;
Keywords: Obsessive-Compulsive Disorder, Cortico-Cerebellar Circuits, Executive Control Network, Functional Connectivity

T28. Using Tolerance Intervals to Capture Heterogeneity in Neurobiological Abnormalities Within PTSD Patients

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Background: A major challenge in studying PTSD is its clinical heterogeneity, which is likely underlined by various neurobiological abnormalities. This heterogeneity limits the ability to study the disorder using standard group-comparison approaches. Here we propose using statistical tolerance intervals (TIs) calculated on the control population to detect patterns of abnormality in patients. We explore the usage of TIs for identifying distinct neural signatures characterizing subpopulations within patients.
Methods: resting state fMRI was recorded from 97 PTSD-diagnosed and 146 healthy combat veterans. Data were preprocessed using FSL, and mean time series was extracted for 133 brain regions. Pairwise functional connectivity (FC) was calculated using Pearson correlation and averaged for each region to obtain a measure of FC to each of 7 previously-defined resting networks, yielding 937 features. TIs were used to select features based on increased abnormality within patients. Patients were then clustered using the selected features in order to examine features ability to capture heterogeneity within patients.
Results: 53 features showed increased abnormality within patients using TIs. Only 6 of these were found in the set of 60 features identified with a two-sample t-test (alpha=0.05). A clustering analysis applied on these features revealed two patient groups that significantly differed in their re-experiencing symptoms (p=0.009). A clustering analysis run on the set of t-test-based features revealed a single cluster spanning almost all patients.
Conclusions: TIs are a potentially useful tool for studying neurobiological patterns in complex disorders as they allow identifying features that capture heterogeneity in abnormalities within patients.
Supported By: Steven and Alexandra Cohen Foundation
Keywords: Functional Neuroimaging, Individual Patient Data, Complex PTSD

T29. Hippocampus Volume as Predisposing Risk Factor for Posttraumatic Stress Disorder

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Background: Neural correlates of posttraumatic stress disorder (PTSD) include smaller hippocampal volumes, possibly underlying deficits in contextual fear learning and extinction. Despite earlier longitudinal data, there remains discussion whether these volumetric abnormalities constitute predisposing risk factors for PTSD development, or represent acquired abnormalities as a consequence of PTSD.
Methods: In a prospective study on the role of automatic defensive responses in the development of trauma-related psychopathology, police recruits were tested before (pre-trauma) and after (post-trauma) their first emergency aid experiences as police officers. To investigate whether pre-trauma hippocampal volumes constitute a risk factor for PTSD symptom development, partial correlations were conducted between pre-trauma hippocampal volumes and post-trauma

clinician-rated (CAPS-5) and self-rated (PCL-5) PTSD symptom severity. Covariates included age and intracranial brain volume. Effects of childhood trauma on hippocampus volume and symptom development were also investigated.

Results: Results in 84 police recruits showed that pre-trauma right hippocampal volume was positively associated with post-trauma clinician-rated PTSD symptom severity ($r=0.234$, $p=.035$), but not with self-rated PTSD symptoms. Additionally, childhood trauma was positively associated post-trauma clinician-rated ($r=0.247$, $p=.026$) and self-rated PTSD symptoms (post-trauma: $r=0.312$, $p=.005$; increase from pre-to post-trauma: $r=0.228$, $p=.040$). Pre-trauma hippocampal volumes were not correlated with childhood trauma, and did not mediate the association between childhood trauma and PTSD symptom development.

Conclusions: These results indicate that larger pre-trauma right hippocampal volume and childhood trauma exposure may be independent predisposing factors for PTSD symptom development in first responders, Ongoing longitudinal measurements within this sample will allow us to disentangle predisposing from acquired volumetric abnormalies in PTSD.

Supported By: Netherlands Organization for Scientific Research

Keywords: PTSD - Posttraumatic Stress Disorder, Hippocampus, Subcortical Volume, Prospective Cohort, Childhood Trauma

T30. Effect of Medication Status on the Gray Matter Volume Abnormalities in Obsessive Compulsive Disorder

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Background: Reported structural abnormalities in obsessive compulsive disorder(OCD) have been inconsistent and the effects of concomitant medications cannot be ruled out. Recent meta-analyses have demonstrated effects of medications on the gray matter(GM) architecture in OCD. We report GM abnormalities in a large sample of DSM-IV OCD patients compared with healthy controls(HC)

Methods: Voxel-based morphometry(VBM) analysis was performed on 3-T structural-T1-weighted Magnetic Resonance Imaging(MRI) scans derived from participants recruited from a single center in India. Regional GM volumes were compared between 221 OCD patients (142 unmedicated) with 194 HC. For VBM analyses of the entire sample, age, sex, years of education, medication status and ICV were included as covariates. For the unmedicated sample, similar variables excepting the medication status were used as covariates. The resulting T-maps were thresholded at $p<0.001$(uncorrected) with cluster extent of 100 followed by small volume correction (SVC) of 10mm sphere.

Results: OCD patients had significantly deficient GM volume corresponding to right middle occipital gyrus and right anterior lobe of cerebellum, while greater volumes were observed in right thalamus, left caudate and left cuneus. Unmedicated patients compared to HC had similar findings but for the additional involvement of left thalamus and left medial geniculate body and lack of difference in caudate volume. Medicated patients on the other hand had significantly reduced volume of left anterior cingulate cortex(ACC) and left medial frontal gyrus.

Conclusions: The classical structural abnormalities reported in OCD involving pre-frontal structures seem to be largely driven by concomitant medication use. Unmedicated OCD patients seem to have abnormalities in regions outside the conventionally described pre-frontal regions.

Supported By: Department of Science and Technology, Government of India; Department of Biotechnology, Government of India; Wellcome trust DBT India Alliance

Keywords: Obsessive Compulsive Disorder (OCD), Voxel-Based Morphometry, Gray Matter Volume

T31. Multimodal Study of Microstructure, Neural Function and Metabolism in Dorsal and Ventral Circuits of Obsessive-Compulsive Disorder

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Background: Few studies to explore white and grey matter microstructure abnormalities in dorsal and wentral circuit of classic CSTC circuit, and also few researches investigated the correlational features between functional and neurochemical alterations in this circuit.

Methods: 100 OCD and 90 HCs were recruited to explore white and grey matter microstructure abnormalities in this circuit with DKI and DTI. And also, 23 OCD and 23 HCs were recruited to investigate the altered FC in association with glutamatergic dysfunction in this circuit with combing rs-fMRI and 1H-MRS.

Results: For structural findings, OCD patients displayed decrease complexity of grey and white matter fiber structure i.e. bilateral cerebellum posterior lobe, anterior and posterior cingulate in dorsal and ventral circuit. Besides this circuit, we also find structural abnormalities in middle occipital lobe and sub-lobar. For functional findings, besides abnormal FC within this circuit, we also found altered FCs in large-scale networks outside this circuit, including occipital area, limbic and motor systems. The decreased FC between bilateral thalamus and right MOG correlated with glutamatergic signal within thalamus in OCD. Moreover, the FC between right thalamus and right dACC was associated with glutamate level in right thalamus in OCD. All above significant results are set $P<0.05$ with Alphasim correction. Finally, the FC between right hemispheric thalamus and MOG was correlated with patients YBOCS compulsion and total score.

Conclusions: Our findings showed that grey and white matter microstructure abnormalities and coupled intrinsic functional-biochemical alterations existed both within dorsal and ventral circuit and from this circuit to occipital lobe/ sub-lobar in OCD pathophysiology.
Supported By: The National Natural Science Foundation of China (No. 81771460); Scientific Project from Shanghai Health Bureau (No. 201740086); Sub-project of Shanghai Science and Technology Committee "scientific and technological innovation action plan" of science and technology support projects in the medicine and agricultural field (No. 15411950203)

Collaborative innovation research project in translational medicine of Shanghai Jiao Tong University School of Medicine (No. TM201614)

Shanghai Jiao Tong University supported by "the Fundamental Research Funds for the Central Universities" (No. 16JXRZ12)
Keywords: Obsessive Compulsive Disorder (OCD), Diffusion Tensor Imaging (DTI), Diffusional Kurtosis Imaging (DKI), Resting State fMRI, 1H MRS)

T32. PTSD Subtype Identification Based on Resting-State EEG Functional Connectivity Biomarkers

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Background: Grouping all PTSD patients, regardless of differences in their patterns of symptoms or brain circuit connectivity, in the same diagnostic category may interfere with our understanding of post-traumatic psychopathology. Delineation of neurophysiology-based subtypes amongst patients diagnosed with PTSD is important for better understanding the relevant latent dimensions of brain function, as a step towards individualized brain-based optimization of treatment approaches. Moreover, doing so with EEG has the potential of facilitating translation to clinical applications.
Methods: We investigated functional connectivity biomarkers using high-density resting-state EEG to identify potential subtypes. Power envelope-based functional connectivity was determined in 106 PTSD patients and 96 healthy subjects, using source localization. Canonical correlation analysis was used to align connectivity features with multiple symptom measures to define a low-dimensional representation of symptom-related connectivity features. Hierarchical clustering based on these connectivity features was carried out to divide the PTSD patients into biologically distinct subtypes.
Results: The results indicate that the biomarkers learned from EEG connectivity define four subtypes of PTSD with distinct connectivity patterns in central executive network. These subtypes are associated with differing clinical symptoms and differ significantly ($p<0.05$, pairwise t-test) in fMRI-assessed functional connectivity within the ventral attention network.
Conclusions: Our study defines novel PTSD subtypes based on resting-state EEG connectivity biomarkers, which may help better define distinct biological subprocesses contributing to the clinical syndrome and its treatment.
Supported By: Cohen Veterans Bioscience; Stanford Neurosciences Institute
Keywords: EEG, Functional Connectivity, PTSD - Post-traumatic Stress Disorder, Subtypes, Biomarkers

T33. Polyepigenetic Prediction of PTSD Physiology Based on Estrogen Status

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Background: It is well-established that women are more likely than men to develop posttraumatic stress disorder (PTSD) following trauma exposure. One of the proposed biological mechanisms for this difference is estrogen levels, such that higher circulating estrogen appears to be a protective factor. The current study examines how individual genetic variation at the level of DNA methylation in response to estrogen levels confers risk for two physiological intermediate phenotypes of PTSD: fear-potentiated startle (FPS) and heart rate variability (HRV).
Methods: Participants were 95 trauma-exposed women recruited as part of the Grady Trauma Project. Using a novel polyepigenetic risk score, with strong validated predictive power for estradiol status, we examine the association of estradiol-associated DNA methylation with FPS and HRV. For each CpG site, methylation proportion will be modeled as a linear function of estradiol. Adjustments will be made for age, cellular proportions, positional effects and ancestry. FPS and HRV variables were obtained from a fear conditioning paradigm.
Results: We developed a DNA methylation-based predictor of estradiol using random forests (RFs). After dividing the cohort into training (70%) and testing (30%) groups, we identified a set of 153 CpG sites, selected from >18,000 estradiol-associated CpG sites across the genome, that predicts estradiol levels in the testing set with strong correlation ($r=0.82$; $p<2.6e-16$).
Conclusions: These data comprise the first study to examine estradiol associated epigenetic modifications and their combined accuracy in predicting physiological intermediate phenotypes of PTSD. Future studies will address implications for identifying individuals most at risk for developing PTSD.
Supported By: NIH, NIMH, MH096764 (Ressler)
Keywords: Estrogen, PTSD, Fear-potentiated Startle Reflex, Heart Rate Variability, Epigenetics

T34. Dysregulated Inflammatory Related Gene Expression in the Dorsolateral Prefrontal of Individuals With PTSD

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Background: The inflammatory system plays a clear role in the pathophysiology of chronic mental and physical illnesses. Individuals with PTSD, depression, and other fear- and anxiety-related disorders exhibit alterations in circulating inflammatory marker levels, suggesting underlying dysfunction of the innate immune inflammatory system. The relationship between innate immune activation and PTSD has been investigated almost exclusively in the periphery, and has not been extensively explored in human postmortem PTSD brain tissue. Based on the known role of interleukin signaling in PTSD and depression, we investigated interleukin gene expression in the dorsolateral prefrontal cortex (dlPFC) using tissue from the newly established National PTSD Brain Bank (NPBB).
Methods: Gene expression analyses were conducted on post-mortem tissue from the dlPFC from 50 donors: 13 controls, 12 PTSD cases, and 25 depressed cases. RNA was extracted from frozen dlPFC tissue, reverse transcribed to cDNA, and quantitative polymerase chain reaction (qPCR) was performed for IL-1A, IL-1B, IL-6, IL-8, IL-10, IL-13, and IL-15.
Results: We demonstrate significant increases in IL-8 expression for PTSD cases compared to controls ($P<0.01$), and significant decreases in IL-1A for PTSD cases compared to controls ($P<0.01$).
Conclusions: Our results indicate that IL-1A and IL-8 are dysregulated in the dlPFC of a cohort of PTSD subjects compared to controls. These findings further support a role for the immune system in the pathophysiology of PTSD, and indicate that dysregulation of interleukins in the periphery shown in earlier studies are also reflected in the brain itself.
Supported By: FGM's contribution to this work was supported by National Institute of Mental Health award number 5T32MH019836-17. This research was also supported by the VA National PTSD Brain Bank and Merit Review award number I01 BX003477-01A1 from the United States (U.S.) Department of Veterans Affairs to MWL.
Keywords: PTSD - Posttraumatic Stress Disorder, Inflammation, Postmortem Human Brain, Depression, DLPFC

T35. Do SSRIs Modulate Peripheral Inflammation in Generalised Anxiety Disorder?

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Background: The interaction between the immune system and the central nervous system has prompted extensive research interest into immunopsychiatry. The immunomodulating effects of antidepressants on depression have been reported, however, there is no evidence of the immunomodulating effects of antidepressants on anxiety. The aim of the study was to investigate the effects of SSRIs on peripheral inflammatory cytokines in patients with generalised anxiety disorder (GAD).
Methods: A prospective cohort design was employed: 42 patients with GAD were recruited and they were treated with SSRIs for 12 weeks. All participants completed measures of anxiety using Generalized Anxiety Disorder 7-item (GAD-7) scale and the State-Trait Anxiety Inventory (STAI), pro-inflammatory cytokines using enzyme-linked immunosorbent assay (ELISA), and CRP determined by immunoturbidimetric method before and after SSRIs treatment.
Results: Baseline measures of anxiety including both GAD-7 and STAI were significantly reduced ($p<0.01$). Baseline levels CRP and pro-inflammatory cytokines (including IL-1α, IL-2, IL-6, IL-8, IL-12, IFN-γ, and GM-CSF), were significantly reduced after treatment of SSRIs ($p<0.05$ in all cases). In addition, changes of anxiety measures co-vary with the changes of peripheral cytokine levels ($p<0.05$). Regression analysis indicated that CRP and IL-6 were significant predictors for treatment response.
Conclusions: This study is the first to reveal moderate anti-inflammatory effects of SSRIs in patients with GAD, which suggests that SSRIs may owe some of their therapeutic effect to their anti-inflammatory properties. Data from randomized controlled trials assessing anti-inflammatory effects of SSRIs is warranted in further larger studies.
Supported By: Suzhou Science and Technology Development Grant in China
Keywords: Antidepressants, Inflammation, Generalised Anxiety Disorder, Cytokines

T36. The Role of PSD95 and nNOS Interaction in the Regulation of Conditioned Fear: A Novel Target for Treatment of PTSD?

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Background: Stimulation of N-methyl-D-aspartic acid receptors (NMDARs) and the resulting activation of neuronal nitric oxide synthase (nNOS) and nitric oxide (NO) production are crucial for fear memory formation. NMDAR antagonists and NOS inhibitors disrupt fear conditioning but have non-specific effects. In this study, we explore the hypothesis that nNOS and PSD95 interaction is critical for fear memory formation and disrupting this protein-protein interaction will reduce conditioned fear with a better side-effects profile.
Methods: Co-immunoprecipitation, electrophysiology, behavioral paradigms, and RNA sequencing were utilized to investigate the PSD95/nNOS binding in various brain regions and test differential effects of the NMDA receptor antagonist MK801 and PSD95-nNOS interaction disruptor ZL006.
Results: Association of PSD95 and nNOS was increased in the basolateral amygdala (BLA) and the ventral hippocampus (vHP) but not in the medial prefrontal cortex (mPFC) immediately following fear conditioning. Systemic and intra-BLA application of ZL006 significantly attenuated fear consolidation in animals and restricted LTP in acute brain slices. Importantly,

unlike NMDAR antagonist MK801, ZL006 treatment is devoid of adverse effects on locomotion, social interaction, object recognition memory and spatial memory. Fear conditioning altered expressions of 81 genes in the BLA, with only a limited gene changes reversed by ZL006.
Conclusions: Disrupting PSD95/nNOS interaction with ZL006 selectively reduces fear memory and represents a novel treatment approach for fear-related disorders, such as post-traumatic stress. Limited ZL006 effect on gene expression suggests that major effects of the drug may be on post-translational modifications such as nitrosylation which will be examined in future studies.
Supported By: NIMH R21MH104018
Keywords: PTSD - Posttraumatic Stress Disorder, NMDA Receptor, Basolateral Amygdala, Long-Term Potentiation (LTP)

T37. Rapid Anxiolytic Effects of a Serotonin Type 4 Receptor Agonist Involve Prefrontal Cortex-Brainstem Neural Circuit Recruitment

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Background: Benzodiazepines are an effective treatment of anxiety disorders for years, but misgiving over side effects have led to prescribe some antidepressant drugs even though they present a delayed onset of action. Here, we seek to evaluate whether serotonin type 4 receptor (5-HT4R) activation and targeting glutamatergic axon terminals arising from the medial prefrontal cortex (mPFC) in the dorsal raphe nucleus (DRN) may constitute a new way to induce fast anxiolytic effects.
Methods: Anxiolytic-like effects of an acute administration (either i.p. or locally into the mPFC) of a 5-HT4R agonist (RS67333) were examined in male BALB/cJRJ anxious mice and compared to diazepam. To provide evidences that anxiolytic effects of RS67333 are mediated by mPFC-brainstem neural circuit recruitment, in vivo recordings of DRN 5-HT cell firing, cerebral serotonin depletion and optogenetic activation or silencing techniques were performed. One- or two-way ANOVAs were applied as appropriate, followed by Fisher's PLSD post-hoc test.
Results: Similarly, to diazepam, systemic and intra-mPFC RS67333 administration produced fast anxiolytic-like effects. Systemic RS67333 increased DRN 5-HT cell firing. Cerebral serotonin depletion prevented intra-mPFC diazepam and RS67333-induced anxiolytic effects. Optogenetic stimulation emphasized the role of mPFC-brainstem neural circuit in these fast anxiolytic effects. Finally, silencing cortical glutamatergic terminals in the DRN after mPFC infusion or systemic administration of diazepam or RS67333, confirmed that this circuit is recruited for fast anxiolytic effects.
Conclusions: This work provided novel insights into mechanisms underlying rapid anxiolytic activity and suggests that the 5-HT4R may represent a rapid onset therapeutic approach to treat anxiety disorders.
Supported By: NARSAD, Pierre Deniker Foundation
Keywords: Anxiety Disorder, 5-HT4 receptor, Benzodiazepine, Medial Prefrontal Cortex-Brainstem Circuit, Optogenetic

T38. Skin Conductance Response in the Emergency Department Predicts Future PTSD Symptom Severity

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Background: Skin Conductance (SC) is a peripheral measure of sympathetic nervous system activity that can be recorded non-invasively using mobile devices. While increased hyperarousal is a hallmark of PTSD, it remains unclear whether it predicts risk for PTSD.
Methods: We recorded SC response to a trauma interview in the Emergency Department within hours of trauma exposure. eSense for iPad with electrodes attached to the fingers was used to collect SC during administration of the standard trauma interview (STI) in 54 participants. Participants were assessed for PTSD symptom severity at 6 months post-trauma.
Results: SCR during the trauma description immediately post-trauma was significantly associated with PTSD diagnosis 6-months later ($F=44.58$, $p<0.0001$). The AUC for the ROC curve analysis for SCR on PTSD diagnosis was 0.91 ($p<0.0001$) with 95% confidence intervals of 0.807 and 1.00. Lasso regression with elastic net was used to define the optimal model to predict PTSD symptoms at 6-months using demographic, clinical and SCR data. When SCR was included in the model it was the only significant predictor of PTSD symptom severity at 6 months ($F=18.82$, $p<0.0001$).
Conclusions: Recording SCR data with a mobile device at the time of trauma is both feasible and useful for identifying trauma survivors who are at risk of developing PTSD. These data indicate that increased hyperarousal in the peri-traumatic time period may be predictive of the development of PTSD over time.
Supported By: R01 MH094757
Keywords: Neurophysiology, Emergency Room, Trauma, Post-Traumatic Stress Disorder

T39. Valproic Acid-Induced Hyperammonemic Encephalopathy

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Background: Valproic acid has been used in the treatment of epilepsy, bipolar and schizoaffective disorder, dementia-related agitation and neuropathic pain effectively. However, it can elevate blood ammonia levels, which might lead to

clinically significant situations such as hyperammonemic encephalopathy. Valproic acid-induced hyperammonemic encephalopathy may occur in people with normal liver function, despite therapeutic doses and serum levels of VPA.
Methods: Here we present a patient who has been on valproic acid for more than 7 years for treatment of Schizoaffective disorder and dementia-related aggressive behavior, presenting with delirium. A review of the literature of similar reported cases and their management will be included, in addition to discussion of the course and outcome of this case.
Results: Patient developed insidiously fluctuation in attention, and appeared to be sleepy and lethargic for most of the time over the course of several days. Ammonia level testing revealed high ammonia level 68 mumole/L (range is 0-47 mumole/L), despite that liver function enzymes and valproic acid level 95.8 (range is 50-100 MG/L) were within normal ranges. Interestingly, previous research showed that elevations in plasma ammonia levels, as high as 140 mumole/L, were well tolerated, and valproic acid dose reductions were not necessary if not symptomatic.
Conclusions: In conclusion, our work will increase the awareness of valproic acid-induced encephalopathy within normal VPA serum levels, as well as to identify delirium superimposed on dementia in individuals presenting with complex clinical picture.
Keywords: Valproic Acid (VPA), Dementia, Ammonia, Schizophrenia, Schizoaffective Disorder

T40. Resveratrol Improves Cognitive Performance and Endothelial Function by Increasing BDNF Expression and Preventing Oxidative Stress During Experimental Vascular Dementia in Streptozotocin-Induced Diabetic Rats

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Background: Vascular dementia (VD) is the second most common type of dementia after Alzheimer's disease. Several studies have reported that vascular risk factors such as diabetes mellitus (DM) have a role in the development of VD and cognitive decline. Resveratrol has beneficial effects such as antioxidant and neuroprotective properties. The present study was aimed to evaluate the effects of resveratrol on cognitive function and vascular reactivity in diabetes-induced rat model of VD.
Methods: A single dose streptozotocin was used for the induction of diabetes and subsequent VD in rats. Rats from Diabetes+Resveratrol group received resveratrol (20 mg/kg/day, ip) after induction of diabetes for 4 weeks. Cognitive function of the rats was then tested by Morris water maze and passive avoidance tests. After behavioral tests, thoracic endothelial function, endothelial nitric oxide synthase (eNOS) expression, hippocampal brain-derived neurotrophic factor (BDNF) expression were assessed. Superoxide dismutase (SOD) level and NADPH oxidase level in serum and vascular tissue were also tested.
Results: It was shown that DM resulted in learning and memory deficits associated with endothelial dysfunction, decreased expression of eNOS and BDNF, increased NADPH oxidase and decreased SOD levels in the serum and vascular tissue of VD rats. By contrast, resveratrol improved memory deficits, endothelial dysfunction, oxidative stress and neurotrophin expression in VD rat model.
Conclusions: Our data suggest that resveratrol treatment prevents changes in endothelial function, eNOS expression, hippocampal BDNF expression, oxidative stress, and consequently VD in DM rats. (This work was supported by a grant from Kocaeli University Scientific Research Project-BAP2016/41).
Supported By: This work was supported by a grant from Kocaeli University Scientific Research Project-BAP2016/41
Keywords: Dementia, Vascular Dysfunction, Animal Behavior, Learning and Memory, Resveratrol

T41. Graph-Theoretic Correlates of Trait Differences in Emotional Awareness

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Background: Previous studies have suggested that trait differences in emotional awareness (EA) are clinically relevant, and associated with differences in neural structure/function. While multiple leading theories suggest that conscious awareness requires widespread information integration across the brain, no study has yet examined the hypothesis that higher EA corresponds to more efficient brain-wide information exchange.
Methods: 26 healthy volunteers (13 female) underwent a resting state functional magnetic resonance imaging scan, and completed the Levels of Emotional Awareness Scale (LEAS; a measure of EA) and the Wechsler Abbreviated Scale of Intelligence (WASI-II; a measure of general intelligence [IQ]). Using a whole-brain functional region-of-interest (ROI) atlas developed by Shirer and colleagues (2012 [Cerebral Cortex 22(1), 158-165]), we computed several graph theory metrics to assess the efficiency of brain-wide information exchange (using the CONN toolbox; edge threshold of $r = 0.3$).
Results: After statistically controlling for differences in age, gender, and IQ, we observed significant relationships between LEAS scores and 1) average path length ($T = -3.48$, $p = 0.002$), 2) global efficiency ($T = 2.35$, $p = 0.029$), 3) local efficiency ($T = 2.66$, $p = 0.014$), 4) cost ($T = 2.52$, $p = 0.02$), 5) clustering coefficient ($T = 2.37$, $p = 0.027$), and 6) degree ($T = 2.52$, $p = 0.02$) for the collective network of all included ROIs.
Conclusions: These results suggest that individuals with higher EA display more efficient information exchange throughout the brain. This is consistent with the idea that conscious awareness requires global accessibility of represented information.
Keywords: Emotion, Emotional Awareness, Graph Theory, Functional Brain Imaging, Resting State Functional Connectivity

T42. Effects of Genetic Variation in Endocannabinoid Signaling on Fear-Extinction Neural Circuitry in Children and Adolescents

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Background: The endocannabinoid system modulates emotion-related behavior and is implicated in fear-based disorders (e.g., anxiety, posttraumatic stress disorder). Neuroimaging studies in adults have linked genetic variation in endocannabinoid signaling with variation in fear-related neural circuitry. For example, individuals carrying the A allele of the fatty acid amide hydrolase (FAAH) gene (rs324420) - associated with lower enzymatic degradation and higher brain endocannabinoid levels - demonstrate increased resting-state functional connectivity between the amygdala and the ventromedial prefrontal cortex (vmPFC). Previous studies link higher amygdala-vmPFC connectivity with lower anxiety and better extinction recall ability, suggesting that the endocannabinoid system is involved in fear-extinction learning. However, despite evidence that these disorders frequently begin in childhood/adolescence, no studies to date have examined the impact of the endocannabinoid system on fear-extinction neural circuitry in youth.
Methods: 48 youth (ages 6-17 years) completed fear-extinction-learning. Twenty-four hours later, functional magnetic resonance imaging and skin conductance response (SCR) data were collected while completing a test of extinction recall, and during a resting-state condition. Genetic data were collected from saliva for the FAAH rs324420 variant by Taqman Genotyping.
Results: During extinction recall, A-alleles demonstrated lower response in the dorsomedial prefrontal cortex, a region involved in conditioned fear responding, relative to youth with the CC genotype. A-alleles also demonstrated lower SCRs during recall, but this effect did not reach significance ($p = 0.062$). A-alleles demonstrated increased amygdala-vmPFC resting-state functional connectivity.
Conclusions: Genetic variation in endocannabinoid signaling alters fear-extinction related neural circuitry in youth, and may play a role in susceptibility to fear-based disorders.
Supported By: American Cancer Society, National Institute of Mental Health
Keywords: Fear Conditioning and Extinction, Brain Development, BOLD fMRI, Endocannabinoids, Skin Conductance

T43. Developmental Origins of Depression-Related White Matter Properties

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Background: Depression is the leading chronic condition. Still, the mechanisms underlying its development are not well understood. This study aimed to determine white matter properties associated with depressive symptomatology in young adulthood and their developmental origins.
Methods: Diffusion weighted imaging and assessment of depressive symptomatology (Beck Depression Inventory) were conducted in 128 young adults (47% male, age 23-24) from the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ). For a subset of these individuals, the database included information on prenatal stress (n=92), and depressive symptoms during adolescence (n=59 of 15 and n=38 of 19 year olds). Fractional anisotropy (FA) in white-matter tracts was calculated using Explore DTI.
Results: MANOVA showed an interaction between depressive symptomatology and FA in the tracts ($F(17, 2142)=3.74$, $p<0.0001$). Post-hoc linear regressions revealed that more depressive symptoms predicted less FA in the left (beta=-0.22, p=0.015, R2=0.05) and right (beta=-0.22 p=0.015, R2=0.05) cingulum and more FA in the right corticospinal tract (beta=0.18, p=0.047, R2=0.03) and superior longitudinal fasciculus (beta=0.17, p=0.048, R2=0.03). Further analyses assessed whether prenatal stress or depressive symptomatology during adolescence might underlie the altered white-matter properties in young adulthood. Less FA in the left cingulum was associated with more prenatal stress (beta=-0.21, p=0.04, R2=0.04), and more depressive symptomatology at age 15 (beta=-0.25, p=0.05, R2=0.06) and 19 (beta=-0.37, p=0.02, R2=0.13).
Conclusions: We conclude that prenatal stress and depressive symptomatology during adolescence predicts altered white-matter properties associated with depressive symptomatology in young adulthood and point out the importance of early intervention.
Supported By: FP7 (EU)
Keywords: Depression, Diffusion Tensor Imaging (DTI), Cingulum Bundle, Prenatal Stress, Adolescent Depression

T44. Evidence for Common and Unique Brain Structures Underlying Emotion Regulation With Different Strategies and Valence: A Developmental Study

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Background: Previous neuroimaging studies of emotion regulation (ER) have largely been conducted with adults and have focused on decreasing negative emotion. The current work is a large study of adolescents to determine if there is a common set of brain structures that underlies reappraisal-based ER tactics regardless of direction (positive/negative) of regulation and valence (positive/negative) of the emotion.
Methods: 115 healthy adolescent participants underwent fMRI using Human Connectome Project (HCP) compatible scanner sequences while performing a cognitive reappraisal ER task that involved Increase, Decrease, and control

conditions with both positive- and negative-valence visual stimuli. Whole-brain BOLD activity during each phase of the ER task was assessed with the general linear model and permutation tests (FWE-corrected).
Results: As seen in prior studies of adults, a set of cortical regions were active across all task contexts (all $T>3.4$, $p<.05$, corrected for multiple comparisons). However, a larger area of prefrontal cortex activation was observed than in previous reports across task contrasts. Also, ventromedial and ventrolateral prefrontal activation not only was condition-specific, but differed compared to previously-reported adult findings. Several dorsolateral prefrontal and parietal lobe HCP parcels were more active in Decrease than in Increase conditions ($T>4.7$, $p<.05$ corrected).
Conclusions: Adolescents in this study had a more extensive set of common brain regions engaged during reappraisal across different task contexts than seen in prior reports. Activity within these commonly-engaged regions was modulated by certain task contexts. A detailed account of similarities and differences with adult findings will be highlighted and discussed in the context of adolescent maturation.
Supported By: R01MH102854-01A1
Keywords: Emotion Regulation, Brain Maturation, Brain Imaging, fMRI, Human Connectome Project

T45. Individual Differences in Executive Functioning, Emotion Regulation Traits, and Their Neural Correlates During Successful Cognitive Reappraisal

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Background: Theories suggest emotion regulation (ER) relies on capacity for executive cognition, but evidence is largely circumstantial or associational. In this study, we tested whether cognitive capacity mediated the relationship between trait-like ER tendencies and success on a cognitive reappraisal task. fMRI was used to determine if these two types of individual differences engaged the same or different brain regions.
Methods: We administered the Cogstate battery, the Cognitive Emotion Regulation Questionnaire (CERQ), and an ER fMRI task, during which participants increased or decreased emotional reactions to positive and negative IAPS pictures (FDR whole brain-corrected). CERQ item data from $n=112$ adolescents were reduced using PCA to 3 factors (Reappraisal, Rumination, Acceptance). Partial posterior indirect effects were assessed to learn if Cogstate executive scores mediated relationships between ER traits and self-reported ER success.
Results: No mediation effects emerged for regulating negative affect. For augmenting positive affect, the relationship between Reappraisal and ER success was mediated by set shifting ability ($p=.038$), while Acceptance and ER success was mediated by Maze Learning ($p=.042$). fMRI data suggest that Acceptance but not Maze Learning individual differences correlated with activity in left amygdala ($p=.039$) and right anterior cingulate ($p=.035$). There were no neural correlates for set shifting nor Reappraisal.
Conclusions: A propensity for acceptance-based, perspective-taking ER predicts success at increasing positive emotions, particularly for those with better executive function. The neural correlates of these individual differences do not overlap, suggesting the interactive effects of executive cognition and ER traits on successful modulation of emotions are not due to shared brain region(s).
Supported By: R01MH102854-01A1; National Institute of Mental Health
Keywords: Emotion Regulation, Executive Function, Brain Imaging, fMRI, Individual Differences, Adolescence

T46. Neural Correlates of Intolerance of Uncertainty in Youth

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Background: Intolerance of uncertainty (IU) is a transdiagnostic construct marked by distress in the face of insufficient information. High levels of IU are associated with the development and maintenance of maladaptive anxiety and worry. Adolescence is a developmental period characterized by dramatic neural maturation and the onset of anxiety disorders. Previous task-based work in adolescents implicates the dorsal anterior cingulate cortex (dACC) in IU. However, the association between dACC intrinsic functional connectivity (iFC) and IU has not been examined; this is the aim of the current study.
Methods: Sixty-four youth (mean age= 12.12) completed the Intolerance of Uncertainty Scale for Children (IUS-C; Comer et al., 2009) and a six-minute resting state fMRI scan. Group-level analyses were conducted using a random-effects, ordinary least-squares model, including IUS-C scores, and three nuisance covariates (age, sex, and mean FD).
Results: Scores on the IUS-C were negatively associated with iFC between the dACC and a cluster including the posterior insula and the putamen.
Conclusions: Previous research indicates that ACC- putamen connectivity underlies anxious apprehension in adolescents. Further, the posterior insula is important for perceptual and motor processing, which may suggest that decreased dACC-posterior insula connectivity observed here is important for integration of motor movement in salience and threat response in youth. These findings bear significance in contributing to literature evaluating the neural correlates of transdiagnostic risk factors for anxiety in youth.
Supported By: K23MH074821
Keywords: Intolerance of Uncertainty, Transdiagnostic Traits, Developmental Psychopathology

T47. Empathy and Depressive Symptoms During Childhood: An Investigation of Neural Mechanisms Using Resting State Functional Connectivity

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Background: Empathy refers to the understanding and sharing of others' emotions, and comprises cognitive and affective components. High levels of affective empathy and low levels of cognitive empathy have been associated with depression in adults. In addition, functional connectivity within the brain's default mode (DMN) and salience networks (SN), involved in cognitive and affective empathy respectively, has been found to be disrupted in depression. The relationship between empathy and depression has not been examined in childhood, a period of life where understanding risk processes is critical.
Methods: In a sample of 112 community-dwelling 9-10 year olds, we measured empathy traits and mood symptoms using self-report questionnaires and conducted functional connectivity analyses using resting-state fMRI data.
Results: We found (for the first time in children) that affective empathy was positively related to depressive symptoms, while cognitive empathy was negatively related to symptoms. However, analyses investigating associations between cognitive and affective empathy and DMN and SN resting state connectivity (using hubs of the DMN and SN as seeds) revealed no significant relationships.
Conclusions: Due to bias in reporting positive findings, it is important to share these results, which may imply that individual differences in empathy are not associated with DMN and SN functional connectivity in children of this age. However, given that seeds were based on an adult meta-analysis, our future work will continue to explore associations between empathy, depression and resting state functional connectivity using complementary whole-brain analysis techniques.
Supported By: Australian Research Council
Keywords: Empathy, Depressive Symptoms, Children, Resting State Functional Connectivity, Affective Symptoms

T48. A Family-Built Brain: Associations Between Family Environment and Child Behavior and Amygdala Resting-State Connectivity

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Background: (Pre)adolescence is an important period in human development characterized by rapid brain maturation. Studies demonstrate effects of extreme caregiving environments (e.g. institutionalized care) on neural development. Little is known about associations of typical variation in family environment (FE) with brain function.
Methods: This study includes 4325 participants, ages 9-10, from the Adolescent Brain and Cognitive Development Study (data release https://doi.org/10.15154/1412097). Using Structural Equation Modelling with questionnaire items as input, three latent variables (LVs)—demographic information (SES, parental marital status, planned pregnancy), child reported (maternal acceptance, family conflict, parental monitoring), and parent reported (family conflict, parent-child conflict) data—were compiled into a higher-level FE LV (RMSEA=.03, TLI=.90, CFI=.91). Partial correlations correcting for child/parent sex assessed associations between LVs and with child internalizing, externalizing, and prosocial behavior.
Results: FE is strongly correlated with lower level LVs, r=.472, r=.929, r=.649, for the demographic, child, and parent reported LVs, respectively. FE is moderately associated with child reported prosocial (r=.282) and parent reported externalizing and internalizing behavior (r=-.348, r=-.185), whereas child reported and parent reported LVs showed higher correlations with same reporter outcomes (child: r=-.128, r=-.250, r=.344, parent: r=-.221, r=-.392, r=.082, for internalizing, externalizing, and prosocial behavior, respectively). All p-values were $p<.001$. Associations with resting-state connectivity of amygdala-based circuitry are underway.
Conclusions: While associations displayed by the parent and child reported LVs suggest shared method bias, the FE LV shows moderate correlations with both positive and negative child behaviors irrespective of reporter. These data provide a promising foundation for the investigation of associations between FE and amygdala-based connectivity.
Supported By: NWO Rubicon
Keywords: Family Environment, Adolescence, Amygdala, Resting State fMRI

T49. Autism-Specific Maternal Autoantibodies Produce ASD Relevant Behaviors in a Mouse Model

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Background: Immune dysregulation has been noted consistently in individuals with autism spectrum disorder (ASD) and their families, including the presence of autoantibodies reactive to fetal brain proteins in nearly a quarter of mothers of children with ASD versus less than 1% in mothers of typically developing children.
Methods: Utilizing the peptide epitope sequences for LDHA and B, STIP1 and CRMP1, we successfully created an endogenous, antigen-driven mouse model to reflect a constant exposure to the salient autoantibodies throughout gestation in C57BL/6J mice. Resulting male and female offspring were then tested using a comprehensive sequence of behavioral assays as well as measures of health and development highly relevant to ASD.

Results: We found that MAR-ASD male and female offspring MAR-ASD mice engaged in significantly fewer bouts of nose-nose sniffing ($F1,42 = 5.758$, $p = 0.021$), nose-anogenital sniffing ($F1,42 = 5.113$, $p = 0.029$), push-crawl play behavior ($F1,42 = 17.656$, $p < 0.001$), front approach behavior ($F1,42 = 24.727$, $p < 0.001$), and following behavior ($F1,42 = 4.372$, $p = 0.043$), indicating lower levels of social behaviors relative to controls. MAR-ASD offspring (n=22) were found to engage in repetitive self-grooming behaviors for a significantly extended period of time relative to control mice (n=21)($F1,39 = 7.075$, $p = 0.011$). MAR-ASD males emitted significantly fewer total USVs (main effect of treatment: $F1,20 = 13.459$, $p = 0.0015$) compared to adult control males.
Conclusions: The presence of MAR ASD-specific epitope autoantibodies in female mice prior to breeding directly resulted in alterations in a constellation of ASD-relevant behaviors.
Supported By: This study was funded by the NIEHS Center for Children's Environmental Health and Environmental Protection Agency (EPA) grants (2P01ES011269-11, 83543201 respectively), the NIEHS-funded CHARGE study (R01ES015359), and the NICHD funded IDDRC 054 (U54HD079125), and the Hartwell Foundation
Keywords: Autism Spectrum Disorder, Autoantibodies, Mouse Model

T50. Adolescent Omega-3 Fatty Acid Deficiency Impairs Frontostriatal Recruitment Following Repeated Amphetamine Treatment in Rats: A 7 Tesla in Vivo phMRI Study

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Background: Although attention deficit hyperactivity disorder is associated with deficits in the omega-3 fatty acid docosahexaenoic acid (DHA), its role in neuroplastic brain changes that occur following repeated amphetamine (AMPH) treatment are not known. This study used pharmacological magnetic resonance imaging (phMRI) to investigate the impact of repeated AMPH exposure and alterations in brain DHA levels on AMPH-induced brain activation patterns.
Methods: Male rats were fed a diet with preformed DHA (fish oil, FO, n=20), no n-3 fatty acids (Deficient, DEF, n=20), or a control diet fortified with alpha-linolenic acid (CON, n=20) from P21-P90. During adolescence (P40-60), half of each diet group received daily AMPH injections escalated weekly (0.5, 1.0, 2.5, 5.0 mg/kg/d) or saline. Following a 30 d abstinence period regional BOLD responses were determined following an AMPH challenge by phMRI.
Results: In AMPH-naïve rats, the AMPH challenge increased BOLD activity in the substantia nigra and basal forebrain and no diet group differences were observed. In AMPH-pretreated CON and FO rats, the AMPH challenge similarly increased BOLD activation in the bilateral caudate putamen, thalamus, and motor and cingulate cortices. In contrast, BOLD activation in AMPH-pretreated DEF rats was similar to AMPH-naïve DEF animals, and AMPH-pretreated DEF rats exhibited attenuated frontostriatal BOLD activation compared with AMPH-pretreated CON and FO rats.
Conclusions: Chronic escalating AMPH treatment induces enduring frontostriatal recruitment and peri-adolescent deficits in brain DHA accrual impair this response. These findings may have implications for understanding the role of DHA biostatus in the therapeutic efficacy of psychostimulant medications.
Supported By: This work was supported in part by National Institute of Health grants MH107378, DK097599, MH097818, and NCRR UL1 RR026314 to R.K.M.
Keywords: Magnetic Resonance Imaging (MRI), D-amphetamine, Docosahexaenoic Acid (DHA)

T51. Maternal Immune Activation Developmentally Disrupts Hippocampal Excitation/Inhibition Balance in Offspring

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Background: Maternal infection is a risk factor of developmental disorder, such as schizophrenia and autism. Our previous study showed that maternal immune activation of mouse by polyriboinosinic-polyribocytidilic acid (poly I:C) reduced mRNA and protein of myelin basic protein and delayed myelination in hippocampal CA1 area at early postnatal period and impaired sensorimotor gating tested by prepulse inhibition in adulthood. But it is not known about how maternal immune activation physiologically affects hippocampal neuronal activity.
Methods: We electrophysiologically investigated the influence on synaptic transmission of mouse hippocampal CA1 pyramidal cells by prenatal poly I:C treatment with whole cell patch-clamp recordings from brain slices. The recordings were done at two developmental periods, early postnatal period (postnatal day 0 -15) and adulthood (postnatal day 49-70).
Results: The poly I:C treatment decreased excitatory synaptic inputs and inversely increased inhibitory (GABAergic) synaptic inputs onto CA1 pyramidal cell in adulthood. Even in early postnatal period, we found that prenatal poly I:C treatment also reduced excitatory synaptic inputs, and potentially increased GABAergic synaptic inputs, which was uncovered by high potassium-induced neuronal activation.
Conclusions: Maternal immune activation developmentally reduces excitatory / inhibitory balance of hippocampal neuronal circuits from an early postnatal period to adulthood, which could result in net inhibition and poor functional organization and integration of hippocampal circuits.
Supported By: Grant-in-Aid for Scientific Research C
Keywords: Maternal Infection, Hippocampus, Neurodevelopment, E/I Balance, Electrophysiology

T52. Autism-Relevant Behavioral Outcomes in an Antigen-Driven Rat Model of Maternal Autoantibody Related Autism

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Background: Immunoglobulin G (IgG) autoantibodies reactive to fetal brain proteins are present in 23% of mothers of children with ASD, raising the possibility of a maternal autoantibody related (MAR) subtype of ASD. While previous passive transfer animal models have yielded promising results, they did not reflect a constant exposure to the salient autoantibodies throughout gestation, as would be the case in the clinical setting. Here we describe a novel non-passive transfer rat model to directly assess the pathologic significance of prenatal exposure to epitope-specific autoantibodies in generating ASD-relevant behaviors in offspring.
Methods: Prior to breeding, female Sprague Dawley rats were randomly assigned to MAR-ASD (N=6) or CONTROL (N=6) treatment groups. Animals in the MAR-ASD treatment groups received a series of immunizations containing peptide epitope sequences of the 4 primary target proteins of MAR ASD (LDH-A, LDH-B, STIP1, and CRMP1) and adjuvant. Controls received PBS and adjuvant only.
Results: Offspring prenatally exposed to ASD-specific maternal antibodies (N=24) emit fewer ultrasonic vocalizations as pups at postnatal day 12 ($p=<0.05$), spend less time engaged in social interaction as juvenile and young adults ($p=<0.05$), fail to engage in reciprocal juvenile play behaviors ($p=<0.05$) and demonstrate increased self-grooming behavior as adults ($p=<0.05$).
Conclusions: The developmental trajectory of social impairments and repetitive behaviors observed parallels features of human ASD, and lends support to prenatal autoantibody exposure as a risk factor for ASD. These findings contribute to the ongoing efforts towards identification of biomarkers specific to subphenotypes of ASD and the establishment of a highly translatable animal model of ASD.
Supported By: This work as supported by grants from the Landreth Foundation and the Nancy Lurie Marks Family Foundation (Van de Water, PI).
Keywords: Autism Spectrum Disorder, Animal Model, Neuroimmunology, Social Behavior, Rat

T53. Pre- and Perinatal Risk Factors for Autism Spectrum Disorder: An Update

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Background: Autism is a chronic neurodevelopmental disorder characterized by social and language impairments, and stereotyped repetitive patterns of behavior. Prevalence rates of autism have increased markedly worldwide including Israel. While most plausible neurodevelopmental theories of autism focus predominantly on genetic factors, data from epidemiological studies emphasize the importance of non-genetic risk factors for autism. This presentation summarizes current updated knowledge of non-genetic, parental, prenatal, and delivery-related risk factors for autism.
Methods: We collected published findings from epidemiological studies by searching MEDLINE and by screening major journals likely to publish epidemiological studies on this topic. In addition, we present original Israeli and international data on autism risk factors through our own research, using the Israeli national birth and autism registries, and findings from the International Collaboration for Autism Registry Epidemiology (iCARE).
Results: Various parental characteristics, in-utero exposure to certain medications and environmental pollutants, and obstetric conditions, appear to be associated with an elevated risk of autism. For instance, results from our study have shown that advancing paternal and maternal age, parental age difference, delivery by cesarean section, and birth weight, have all been associated with increased risk for autism.
Conclusions: Findings from epidemiological studies suggest that exposure to several parental, prenatal, and delivery-related factors may increase risk of autism. Identifying modifiable risk factors for autism has important public health and clinical implications, especially in view of the dramatic increase in reported prevalence of autism. Given the inconsistency across studies and populations for some results, and the plausibility of additional yet unrecognized risk factors, large epidemiological, population-based birth cohort studies are of particular importance.
Keywords: Autism Spectrum Disorder, Prenatal, perinatal, Epidemiology

T54. Frequency of Patient Visits With Physician Diagnosed Sexual Abuse (SA) from a Nationally Representative Sample in the U.S.

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Background: Sexual abuse (SA) is a known risk factor for the development of serious psychopathology and psychosomatic syndromes. The surveys of SA from nationally representative samples in the US have been community-based and retrospective or involved special groups. We examined the frequency of physician-diagnosed SA from nationally representative US samples of patient visits to physicians' offices, and hospital outpatient (OPD) and emergency departments (ED).
Methods: We examined data from the National Ambulatory Health Care Survey and the OPD and ED and visits in the National Hospital Ambulatory Care Survey from 1995-2014. The 'Sexual Abuse' (SA) variable consisted of the following: 'reason for visit' codes: 5830.0 Rape, and 5830.1 Sexual abuse; and ICD9-CM codes: 995.53 Child sexual abuse, 995.83 Adult sexual abuse, 960.1 E-code Rape, and V71.5 Observation following alleged rape or seduction.
Results: There were an estimated (±SE) 5,623,551±652,158 (% total visits: 0.03%± 0.003%) patient visits for SA (mean±SE age:19.07±1.02 years; 79.4%±3.4% female). The pediatric age group (≤18 years) accounted for 66.2%±3.4% of all SA visits. There was no change in the frequency of SA visits from 1995 to 2014 among the children (OR=0.901,95% CI 0.508-1.599) or adults (OR=0.862, 95% CI 0.561-1.324). Payment

type was more likely to be Medicaid: OR=3.088 (95% CI 1.777-5.365).
Conclusions: The majority of the SA visits involved economically deprived children, which constitutes a highly vulnerable group. There was no significant change in the frequency of SA-related visits over the past 2 decades, even though the actual frequency of 0.03% is probably a gross under-representation of the true SA prevalence.
Keywords: Sexual Assault, Epidemiology, Pediatrics, Child Abuse, Socioeconomic Factors

T55. Developmental Trajectory of Scalp to Cortex Distance: Implications of Transcranial Magnetic Stimulation in Adolescents With Major Depressive Disorder

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Background: Brain stimulation is increasingly used as a probe of function and intervention in pediatric populations. The distance between the scalp and the cortex is an important variable as the signal is attenuated by distance. To date, there have been no investigations of the influence of age on scalp to cortex distance in youth with neuropsychiatric disorders.
Methods: Forty-eight youth with depression (MDD, 13 - 24 years, 26 males, 22 females) and 30 healthy controls (12 males, 18 females) underwent magnetic resonance imaging (MRI) scans on a 3.0 T scanner. Distance measurements were obtained using FreeSurfer and AFNI. Sites were the left dorsolateral prefrontal cortex (DLPFC) and dominant primary motor cortex (M1). We set $p < 0.01$ to control for multiple comparisons.
Results: Scalp to cortex distance for the DLPFC demonstrated a trend for greater distance in adolescents with MDD compared to healthy adolescents ($t = -1.97$, $p = 0.05$) with no difference in M1 ($t = -0.65$, $p = 0.52$). However, scalp to cortex distance for the DLPFC and age was positively correlated in healthy adolescents ($r = 0.61$, $p = 0.0005$, 37% of the variance) but not in adolescents with MDD ($r = 0.14$, $p = 0.38$). A trend for M1 distance and age was observed controls ($r = 0.47$, $p = 0.02$) and MDD ($r = 0.30$, $p = 0.08$).
Conclusions: Age differentially influences scalp to cortex distance in youth with MDD as compared to healthy youth. This has implications for the application of brain stimulation in pediatric samples.
Supported By: Canadian Foundation for Innovation, Alberta Children's Hospital, Alberta Health Services
Keywords: Repetitive Transcranial Magnetic Stimulation, Dorsolateral Prefrontal Cortex, Adolescent Depression, Developmental Trajectories, Motor Cortex

T56. Brain Functional Connectivity in Neonates With Prenatal Opioid Exposure: A Preliminary Study Focusing on the Amygdala

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Background: Rates of opioid use in pregnancy have increased dramatically in the past decade and understanding the relationship between prenatal opioid exposure (OE) and postnatal brain and behavioral development represents a critical public health topic. Here, neonates with or without OE were recruited and evaluated using resting-state fMRI (rsfMRI). We focused on the amygdala given its central role in arousal regulation, which is reportedly disrupted in neonates with OE.
Methods: Neonates ($N = 139$) with rsfMRI and pertinent participant characteristics were included in this study. Amygdala seed-based functional connectivity analysis was conducted with permutation-cluster based thresholding. Subjects (OE, non-OE but other drug exposure (NOE), and CTR) were matched based on drug exposure, race, postnatal age, birth weight, motion, scanner, and maternal education/depression.
Results: Six clusters demonstrated significant group main-effects ($P < 0.05$, corrected). Post-hoc analyses revealed predominantly OE-specific effects; left amygdala with [1] right insula: OE > NOE > CTR ($P < 0.001$), [2] left post-central gyrus: OE < NOE ≈ CTR ($P = 0.002$), [3] right middle temporal gyrus (MTG): OE > NOE ≈ CTR ($P < 0.001$), [4] left MTG: OE > NOE ≈ CTR ($P < 0.001$), and right amygdala with: [5] left MTG: OE > NOE ≈ CTR ($P < 0.001$), [6] right MTG: OE > NOE ≈ CTR ($P < 0.001$).
Conclusions: We demonstrated significant associations between prenatal OE and amygdala functional connectivity, including regions related to salience processing, sensorimotor, and language functions. These data suggest dysconnectivity between the amygdala and other brain structures could mediate OE-related neurodevelopmental deficits.
Supported By: 1R03DA036645-01A1, 1R21DA043171-01
Keywords: Brain Imaging, fMRI, Resting state Functional Connectivity, Prenatal Opioid Exposure, Amygdala, Neonatal Imaging

T57. Abnormal Development of Amygdala Functional Connectivity During Emotion Processing in Pediatric Post-Traumatic Stress Disorder

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Background: Pediatric post-traumatic stress disorder (PTSD) in youth is characterized by abnormal emotion processing related to trauma-exposure and has been associated with abnormal amygdala-prefrontal function in cross-sectional studies. However, little is known about the development of amygdala functional connectivity in afflicted youth from a longitudinal perspective.
Methods: In this naturalistic longitudinal study, we examined developmental changes in emotion processing-related amygdala functional connectivity in 23 medication-free youth with PTSD (ages 8-18 at baseline) compared to 21 non-traumatized, healthy comparison youth (HC), matched for age and sex. All youth underwent a trauma and psychiatric screen and fMRI during implicit processing of emotional facial expressions, completed at initial evaluation and one-year follow-up.

Linear mixed-effects regression was conducted to examine group (PTSD v. HC) differences in the development of functional coupling with amygdala subnuclei.
Results: In group x age interactions, the right centromedial nucleus showed abnormal functional coupling with the left posterior hippocampus ($t[20] = 3.46$; $p = 0.03$) and bilateral dorsal anterior cingulate cortex (dACC; $t[20] = 5.50$, $p < 0.01$) during emotion processing. Within both circuits, PTSD youth displayed decreased coupling with age, whereas HC youth showed no change.
Conclusions: These findings represent the first known longitudinal investigation of task-based functional connectivity in trauma-exposed youth. Notably, age-related abnormalities in these circuits were observed only when modelled longitudinally and absent in cross-sectional analyses within this same sample. This highlights the importance of longitudinal designs when studying developing populations and adds to the growing body of evidence supporting the relevance of amygdala functional development in PTSD-related pathophysiology.
Supported By: NIMH (RJH; K08 MH100267), NIH/NCATS (RJH; UL1TR000427), NRSA (TJK; GM007507), NSF (TJK; DGE-1747503)
Keywords: PTSD - Posttraumatic Stress Disorder, Childhood Trauma, Amygdala, Functional Brain Imaging, Child and Adolescent Psychiatry

T58. Attentional Control and Fronto-Parietal Connectivity in Pediatric OCD

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Background: Cognitive control and attentional processes may be altered in pediatric obsessive-compulsive disorder (OCD) due to altered functional connectivity within the fronto-parietal control network. To date, resting state functional connectivity (RSFC) within this network has not been assessed in unmedicated youth with OCD.
Methods: Resting state fMRI scans were acquired from 24 children/adolescents with OCD (age: M=12.8 years, SD=2.7) and 20 age- and sex-matched healthy youth (age: M=11.6 years, SD=2.8). Seed-to-voxel analyses were used to assess group differences in RSFC from fronto-parietal seeds to whole brain. Exploratory analyses assessed associations of fronto-parietal RSFC and attentional control on the Continuous Performance Task (CPT).
Results: Compared to healthy youth, those with OCD showed significantly less RSFC from left inferior parietal lobe (IPL) to bilateral precentral and postcentral gyri ($p<0.001$). Youth with OCD also exhibited more commission errors ($p=0.003$), shorter reaction times ($p=0.004$), and worse detectability ($p=0.028$) during the CPT. Lower RSFC from left IPL to right postcentral gyrus was associated with more CPT commission errors in the OCD group ($r = -0.535$, $p=0.007$). Further, this connectivity mediated group differences in commission errors (b=3.93, 95% CI=0.26-8.25) and detectability (b=4.62, 95% CI=1.75 - 8.87).
Conclusions: Fronto-parietal functional connectivity is altered in youth with OCD, perhaps contributing, in part, to their deficits in cognitive control processes. These findings suggest that the fronto-parietal network might be a target for future clinical trials aimed at preventing OCD symptoms via attentional control training.
Supported By: R21MH101441
Keywords: Pediatric OCD, Attentional Control, Resting State fMRI, Fronto-Parietal Network

T59. Does White Matter Microstructural Integrity Differ in the Combined and Inattentive Subtypes of ADHD? A Diffusion Tensor Imaging Study

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Background: Converging evidence indicates that dysfunctional brain network connections are concordant with aberrant neuroanatomical and functional features; these findings extend support for differential neural mechanisms underlying the ADHD subtypes. However, diffusion tensor imaging (DTI) studies investigating microstructural white matter (WM) properties between the ADHD subtypes are limited and have shown equivocal results.
Methods: We used DTI data from 35 ADHD participants defined using DSM-IV criteria as combined (n=19) or as predominantly inattentive type (n=16), aged 8-17 years, and 28 matched neurotypical controls. We performed tract-based spatial statistical (TBSS) analyses on DTI derived measures of fractional anisotropy (FA), mean (MD), radial (RD), and axial (AD) diffusivity to assess differences in WM microstructural integrity between the two ADHD subtypes and controls.
Results: DTI measures (FA, MD, RD, and AD) were not found to differ significantly between the ADHD subtypes, or for each subtype relative to controls. This null finding was observed in the context that the same ADHD subtypes were distinguished by grey matter organization, as quantified by structural covariance.
Conclusions: Adding to the paucity of DTI studies examining ADHD subtypes, this study did not observe WM differences that may distinguish the ADHD subtypes. Given our observation of grey matter disorganization in the absence of loss of white matter integrity, anatomical network patterns may better account for the clinical symptoms that characterize the ADHD subtypes.
Keywords: ADHD, Diffusion Tensor Imaging (DTI), White Matter Integrity, Tract Based Spatial Statistics (TBSS), ADHD Subtypes

T60. ADHD and the Cortex: Evidence From Large Clinical and Population Based Samples

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Background: Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD. However, these studies are often underpowered and heterogeneous in their methods. Here, we present data from large-scale clinical and population-based samples to study links between ADHD and the cortex.
Methods: For 2259 cases and 1938 controls (ENIGMA-ADHD) and 2707 children (Generation-R) cortical thickness and surface area of 34 regions was calculated (Desikan-Killiany atlas). Case-control differences in children, adolescents and adults were assessed, and effects of clinical measures (e.g. comorbidity) were studied. In the Generation-R sample, the association between cortical measures and CBCL-scores (attention/ADHD) was analyzed. Also, familial effects on the cortex were studied.
Results: Children with ADHD showed smaller surface area values in various regions of the brain (e.g. total surface area, d= -0.25, pFDR=2.21E-07). Thickness of fusiform gyrus and temporal pole (both d=-0.22, pFDR=1.2E-07) were thinner in ADHD children versus controls. No differences in adolescents/adulthood, and a limited contribution of clinical features were found. In Generation-R, CBCL-scores were associated with clinically-affected surface area values, pFDRE<0.05. Familial effects were found for total and lateralorbitofrontal surface area, and fusiform thickness.
Conclusions: Only children, but not adolescents and adults with ADHD had reduced surface area (global) and cortical thickness (temporal lobe). Surface area abnormalities were also associated with ADHD traits in a normal pediatric population. Our population and familiality analyses indicate a familial, either genetic or environmental, nature of these differences; they do not seem to be a mere consequence of living with ADHD.
Supported By: ENIGMA received funding from the National Institutes of Health (NIH) Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centers of Excellence (BD2K). We also are supported by the Netherlands Organization for Scientific Research (NWO) and the European College for Neuropsychopharmacology (ECNP) Network ADHD across the lifespan.
Keywords: Cortex, ADHD, Cortical Surface Area, Familiality, Cortical Thickness

T61. Neural Correlates of Taste Reactivity in Autism Spectrum Disorder

Jason Avery[1], John Ingeholm[1], Sophie Wohltjen[1], Meghan Collins[1], Cameron Riddell[1], Stephen Gotts[1], Lauren Kenworthy[2], Gregory Wallace[3], W. Kyle Simmons[4], and Alex Martin[1]

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Background: Selective or 'picky' eating habits are common among those with autism spectrum disorder (ASD). These behaviors are often related to aberrant sensory experience in individuals with ASD, including heightened reactivity to food taste and texture. However, very little is known about the neural mechanisms that underlie taste reactivity in ASD.
Methods: 21 young adult and adolescent males diagnosed with ASD without intellectual disability, and 21 typically-developing (TD) controls were evaluated. Taste reactivity was assessed using the Adolescent/Adult Sensory Profile, a clinical self-report measure. Functional magnetic resonance imaging was used to evaluate neural responses to sweet (vs. neutral) tastants and food pictures. Subjects also underwent resting-state functional connectivity scans.
Results: The ASD and TD individuals did not differ in their hemodynamic response to gustatory stimuli. However, the ASD subjects, but not the controls, exhibited a positive association between self-reported taste reactivity and the response to sweet tastants within the insular cortex and multiple brain regions associated with gustatory perception and reward. There was a strong interaction between diagnostic group and taste reactivity on tastant response in brain regions associated with ASD pathophysiology, including the bilateral anterior superior temporal sulcus (STS). This interaction of diagnosis and taste reactivity was also observed in the resting state functional connectivity between the anterior STS and dorsal mid-insula (i.e., gustatory cortex).
Conclusions: Self-reported heightened taste reactivity in ASD is associated with heightened brain responses to food-related stimuli and atypical functional connectivity of primary gustatory cortex, which may predispose these individuals to maladaptive and unhealthy patterns of selective eating behavior.
Supported By: National Institute of Mental Health Intramural Research Program (ZIAMH002920)
Keywords: Autism Spectrum Disorder, Gustation, Brain Imaging, fMRI, Insula

T62. A Haplotype of the Norepinephrine Transporter Gene Modulates White Matter Integrity in Children With Attention-Deficit/Hyperactivity Disorder

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Background: The norepinephrine transporter gene (SLC6A2) and movement time deficits have been consistently reported to

be associated with attention-deficit hyperactivity disorder (ADHD). This study aimed to examine whether the SLC6A2 rs36011 (T)/rs1566652 (G) haplotype affected white matter (WM) structural property in children with ADHD and whether those alterations were associated with movement time deficits.
Methods: A total of 66 drug-naïve children with ADHD and 80 typically developing (TD) children were recruited. Movement time was assessed by the Reaction Time (RTI) task. After acquisition of the diffusion spectrum imaging (DSI), whole brain tractography was reconstructed by a tract-based automatic analysis. Radial diffusivity (RD) values were computed to indicate tract-specific WM property with adjusted p value $<$ 0.05 for false discovery rate correction (FDR). We examined the effects of diagnosis, haplotype, and the diagnosis-haplotype interaction on the RD values of the WM tracts.
Results: Among 76 WM tracts over the entire brain, ANOVA with FDR correction demonstrated that the TG carriers showed significantly lower mean RD values in the left uncinate fasciculus ($q = 0.038$) than the non-carriers. In the ADHD-TG group, we found that the RD mean value in the left uncinate fasciculus was positively correlatively with RTI movement time ($r = 0.46$, $p = 0.015$).
Conclusions: A novel gene-brain-behavior association was identified in which the microstructural property of the left uncinate fasciculus was related to movement time performance in ADHD children with the SLC6A2 rs36011 (T)/rs1566652 (G) haplotype.
Supported By: NSC99-2321-B-002-037
Keywords: Adults With a Childhood Diagnosis of Attention Deficit/Hyperactivity Disorder, Diffusion Spectrum Imaging, Gene

T63. Parsing Attention Dysfunction in Children With Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder

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Background: Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) frequently co-occur. One approach to study this comorbidity, is through the exploration of convergent symptoms. Aberrant attention, a core feature of ADHD, is widely present in ASD. Despite evidence of aberrant attention in ASD, the underlying mechanism/s and its correlation to ADHD is poorly understood.
Methods: Sixteen children with ASD (mean age 8.3, SD 1.3) were included in this study. All children met DSM-5 criteria for ASD. In addition, all participants were evaluated for ADHD. Standardized measures of cognitive and adaptive functioning were obtained. Parents completed the Swanson Nolan and Pelham Questionnaire (SNAP) and Child Behavior Checklist (CBCL). Finally, all children completed the Attention Network Test (ANT) and a gap-overlap eye-tracking paradigm.
Results: Half of the participants met diagnostic criteria for ADHD. There was no difference in baseline demographic factors. Children with comorbid ADHD performed worse on VABS-2 ($p=0.03$). Neither the SNAP nor the CBCL captured symptoms of ADHD accurately. Nonetheless, statistical differences in subscales suggestive of hyperactivity were noted (all $p<0.01$). Statistical differences in the ANT for the orienting ($F(2,13)=18.82$, $p=0.0001$) and executive ($F(2,13)=4.60$, $p=0.0308$) networks were found. Finally, individual social disengagement times were inversely correlated to adaptive scores.
Conclusions: Our results suggest that commonly used clinical instruments might prove deficient when assessing for ADHD in children with ASD. Objective measures of attention, as the ANT and eye-tracking, are alternatives that might offer important insights into the nature of this comorbidity.
Supported By: AACAP, KTGF
Keywords: Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Attention Network Test, Eye Tracking

T64. An Experience Sampling Study of Emotional Dysregulation in Adults With Attention-Deficit/Hyperactivity Disorder and Borderline Personality Disorder

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Background: There is ongoing debate about the overlap between Attention-Deficit/Hyperactivity Disorder (ADHD) and Borderline Personality Disorder (BPD), mostly in regards to emotional dysregulation (ED). ED, characterised by rapid and exaggerated changes in emotional states, is an associated feature in ADHD and a core symptom in BPD.
Methods: Experience sampling methodology (ESM) was used in an all-female sample of ADHD ($n=28$), BPD ($n= 20$), comorbid ADHD/BPD ($n=22$) and psychiatric controls ($n=29$) to obtain repeated assessments of ED without relying on retrospective recall. Reports of positive and negative emotions were completed eight times daily for five days. Group differences in emotional intensity and instability were investigated, and how ESM and questionnaire measures of ED (Affective Lability Scale-ALS) correlated.
Results: Patterns of intensity and instability of negative emotions (irritable, frustrated, angry) are similar in ADHD, BPD and ADHD/BPD ($p>0.5$). Similarly, all clinical groups showed heightened instability of emotions on the ALS, with each only being significantly different from the control group ($p<.001$). A small to moderate negative correlation ($r=-.3$, $p<.05$) and a large positive correlation ($r=.57$, $p<.001$) were found between positive indices of EL from ESM and the ALS, and negatives indices of EL from ESM and the ALS respectively.
Conclusions: In this first direct ESM comparison of ED, females with ADHD, BPD and ADHD/BPD did not differ in the intensity and instability of negative emotions- further validated by the self-rated questionnaire. Correlations show that ambulatory monitoring are complementary to rating scale measures, and can offer an independent contribution to the understanding of the dynamics of emotions.
Supported By: Other
Keywords: Adult ADHD, Borderline Personality Disorder, Experience Sampling, Mood Instability

T65. Electroconvulsive Therapy for Manic State With Mixed and Psychotic Features in a Teenager With Bipolar Disorder and Comorbid Episodic Obsessive–Compulsive Disorder: A Case Report

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Background: Comorbidity of bipolar disorder and obsessive-compulsive disorder is common in adolescence. Obsessive-compulsive disorder symptoms may be episodic and secondary to alterations in mood. Management of pediatric bipolar disorder-obsessive-compulsive disorder is challenging, as pharmacotherapy of obsessive-compulsive disorder may induce or exacerbate manic episodes and there is limited evidence of treatment efficacy. Electroconvulsive therapy is sparsely used in adolescents, but is documented to be a safe and efficacious intervention in adults with bipolar disorder. In view of severity of symptoms in juvenile mania, studies on treatment strategies are warranted.
Methods: A 16-year-old girl of middle east origin first presented with depressed mood, irritability, and increased obsessive-compulsive disorder symptoms. She had been diagnosed with bipolar disorder and obsessive-compulsive disorder in her previous home country. During hospitalization her mood switched to a manic state with mixed and psychotic features. Interruption in lithium treatment for a short period and possibly the introduction of an atypical antipsychotic could in part have been triggering factors.
Results: After 8 weeks of in-patient care and psychotropic drug trials, electroconvulsive therapy was administered for 4 weeks, with marked positive response.
Conclusions: This case demonstrates the need for a detailed medical history, taking special note of periodicity and character of obsessive-compulsive disorder symptoms, in adolescents with mood disorders. Special concerns in the pharmacological treatment to avoid the patient's condition from worsening must be addressed, including giving priority to mood stabilization before obsessive-compulsive disorder symptoms. There are potential benefits in considering electroconvulsive therapy in young patients with severe mania where first-line treatment options have failed.
Keywords: Electroconvulsive Therapy (ECT), Child and Adolescent Psychiatry, Bipolar Disorder, Obsessive Compulsive Disorder (OCD), Psychiatric Comorbidities

T66. Arousal Profiles in Young Individuals With ADHD as a Function of Recording Context

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Background: A recent study found that attention-deficit/hyperactivity disorder (ADHD) was associated with hypo-arousal during a low-demand reaction-time task, which normalised in a fast-incentive condition. We now investigate if arousal in individuals with ADHD changes over a long testing session, to clarify if atypical arousal profiles are context-dependent. We also examine how arousal relates to each ADHD symptom domain, and the specificity of arousal profiles to ADHD, by controlling for oppositional defiant/conduct disorder (ODD/CD) symptoms.
Methods: Skin conductance level (SCL) and non-specific fluctuations (NSFs) were measured during four successive conditions (Resting-state time 1; Continuous Performance Task[CPT]; Four-choice reaction time task [Fast Task baseline condition]; Resting-state time 2) from 71 adolescents/young adults with ADHD and 140 controls.
Results: Regression models showed that individuals with ADHD did not differ from controls during the initial two conditions, whereas they showed higher NSFs during both the Fast Task and Resting-state time 2 ($p<.05$), and had lower SCL during the Fast Task (as reported previously). Despite a significant case-control difference in NSFs during Resting-state time 2 but not time 1, the group-by-time interaction was significant only after controlling for ODD/CD. Both inattentive and hyperactive-impulsive symptoms were significantly associated with lower SCL (B=-3.42-3.19) and increased NSFs (B=2.31-2.81), independently from ODD/CD symptoms.
Conclusions: Lower arousal was observed in individuals with ADHD during a slow, low-demanding task, and more fluctuating arousal emerged over time, towards the end of assessment when controlling for ODD/CD. We extend previous findings by showing that under-arousal, but also fluctuating arousal, are context-specific rather than stable impairments in ADHD.
Supported By: UK Medical Research Council; Action Medical Research and the Peter Sowerby Charitable Foundation; NIMH.
Keywords: Autonomic Nervous System, Skin Conductance, ADHD

T67. Is Increased Response Time Variability Related to Deficient Emotional Self-Regulation in Children With ADHD?

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Background: Elevated reaction time intra-subject variability (RT-ISV) characterizes Attention-Deficit/Hyperactivity Disorder (ADHD). Deficient emotional self-regulation (DESR), defined by adding Child Behavior Checklist Anxious/Depressed, Aggressive Behavior, and Attention Problems subscale scores, has

been associated with worse outcome in ADHD. To determine if DESR is differentially associated with elevated RT-ISV, we examined RT-ISV in children with ADHD with and without DESR and in typically developing children (TDC). If DESR were related to increased RT-ISV, the latter could be used as a neuropsychological marker to help identify children with ADHD at higher risk for poor outcome, with potential clinical value.
Methods: We contrasted RT-ISV during a 6-min Eriksen Flanker Task in 31 children with ADHD without DESR, 34 with ADHD with DESR, and 65 TDC. Mean response time, RT standard deviation, RT coefficient of variation, and ex-Gaussian parameters were computed for each subject.
Results: Regardless of DESR, children with ADHD showed significantly greater RT-ISV than TDC ($p<0.001$). The two ADHD subgroups, defined by presence or absence of DESR, did not differ from each other.
Conclusions: Increased RT-ISV characterizes ADHD regardless of comorbid DESR. Along with a similar finding in adults with ADHD, these results suggest that RT-ISV is domain-specific rather than domain-general, I.e., related to cognitive rather than emotional dysregulation in ADHD.
Supported By: This project was partially supported by the endowment provided by Phyllis Green and Randolph Cowen, grants from the Leon Levy Foundation, and NIH (K23MH087770 to ADM; R01MH081218, R01HD065282 to FXC).
Keywords: Attention-Deficit/Hyperactivity Disorder, Reaction Time Variability, Deficient Emotional Self-regulation, Intra-individual Variability, Emotional Dysregulation

T68. Hope and Borderline-Personality Disorder as Predictors of Study Drop-Out Among Inpatient Youth Receiving Psychotherapy Treatment for an Episode of Deliberate Self-Harm

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Background: Youth is a known high-risk time for deliberate self-harm (DSH; non-suicidal self-injury and suicide attempts). Despite there being a clear need for effective psychological treatments for youth admitted following DSH, there is limited data on which treatments are most effective and mediators of adherence. The objective of this study was to determine whether hope and/or borderline-personality disorder (BPD) predict study drop-out rates among youth admitted for an episode of DSH.
Methods: Twenty youth participants ages 15-25 ($M= 18.25$, $SD= 3.02$) recruited from the psychiatry inpatient unit of a university-affiliated hospital were included in this analysis. Participants were randomized to receive 10 sessions of either cognitive-behavioural therapy (CBT) for suicide prevention or minimally-directive supportive therapy. Participants completed the Adult Hope Scale self-report measure at baseline and were divided into two groups based on hope score at baseline. A Mann-Whitney U Test was conducted.
Results: Seven of nine study drop-outs had BPD/BPD traits (78%), while 0 of 11 completers had BPD/BPD traits ($U= 7.00$, $p< 0.0001$). Participants who dropped out of the study had a mean baseline hope score of 29.44 ($SD= 8.66$; "low hope") versus participants who were not study drop-outs who had a mean baseline hope score of 39.18 ($SD= 7.37$; "high hope"), $U= 29.00$, $p= 0.07$.
Conclusions: Participants with a diagnosis of BPD/BPD traits and with low hope were much less likely to stay in treatment. Future studies of CBT for suicide prevention should account for these differences and consider a different/modified treatment approach for those with low hope or BPD.
Supported By: The Innovation Fund of the Alternative Funding Plan from the Academic Health Sciences Centres of Ontario.
Keywords: Youth, Deliberate Self-Harm, Psychotherapy, Borderline-Personality Disorder, Hope

T69. Dissociative Subtypes of Detachment and Compartmentalization are Associated With Different Neural Activity in a Masked Fearful Face Paradigm

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Background: Dissociative symptoms include both detachment from experience (e.g., depersonalization/derealization) and compartmentalization (i.e., deficit in volitional control over processes that are ordinarily controllable). Differential brain activation has been identified in individuals with posttraumatic stress disorder (PTSD) who have high vs. low levels of detachment dissociation in symptom provocation paradigms. However, investigation has largely been limited to this single paradigm and detachment dissociation. We sought to examine the neural correlates of both types of dissociation in a non-trauma related paradigm.
Methods: Participants were a cross-diagnostic cohort of women with histories of childhood maltreatment ($N=29$). Participants completed diagnostic interviews, a self-report of dissociation, the Multidimensional Inventory of Dissociation, and an MRI scan that included a masked fearful faces task. During the task, participants made a gender judgment about neutral mask faces. Unbeknownst to participants, fearful and neutral faces were presented before the mask faces.
Results: Preliminary fMRI ROI analyses probed the fearful>neutral face contrast ($p's<.015$ uncorrected) after controlling for PTSD symptom severity. Higher detachment dissociation was associated with more activation in medial prefrontal cortex and midcingulate cortex. In comparison, higher compartmentalization dissociation was associated with less activation in superior frontal gyrus and supplementary motor area.
Conclusions: Detachment dissociation findings replicate symptom provocation findings in a new non-trauma context – supporting a top-down cortical "over regulation" hypothesis of detachment dissociation. We also provide novel evidence that

detachment and compartmentalization dissociation are associated with different neural activity. This highlights the importance of comprehensively assessing dissociative symptoms to better understand their unique biological correlates and treatment outcomes.
Supported By: R21 MH112956; F32 MH109274; Trauma Scholars Fund; Anonymous Women's Health Fund; O'Keefe Family Foundation; Trauma Scholars Fund; Frazier Foundation Grant for Mood and Anxiety Research
Keywords: Dissociation, BOLD fMRI, PTSD - Posttraumatic Stress Disorder, Dissociative Disorder, Fear

T70. Increased Diffusion Kurtosis of Gray Matter in Schizophrenia

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Background: Gray matter (GM) microstructural impairments in schizophrenia (SZ) have been suggested by post-mortem histological studies. However, in vivo examination of these alterations remains to date very limited. In this study, we use three microstructural metrics obtained using a diffusional kurtosis imaging (DKI) approach: mean kurtosis (MK), mean diffusivity (MD) and fractional anisotropy (FA), to non-invasively study GM microstructure in chronic SZ compared to healthy controls (HC). Kurtosis reflects tissue complexity and was shown to be sensitive to GM changes due to both development and pathology.
Methods: DKI and anatomical MPRAGE T1-weighted data was acquired in eighteen SZ patients and nineteen comparison HC (right-handed males, 30-55 years old) on a 3T Siemens MRI scanner. MK, MD, and FA maps were calculated using in-house developed software. Regions of interest were first derived in each subject using Freesurfer and the T1-weighted images and then transferred into the diffusion space. Mean MK, MD, and FA were calculated across GM of all four lobes (frontal, temporal, parietal, and occipital) and for cortical and subcortical regions described by Desikan-Killiany atlas.
Results: Significant increases in MK, MD, and FA ($p<0.05$) in SZ compared to HC participants were found both across all four lobes GM, and in several more localized brain regions previously associated with schizophrenia neuropathology notably thalamus, hippocampus, and dorsolateral prefrontal cortex.
Conclusions: These results suggest pervasive GM microstructural alterations in schizophrenia. Better understanding of these alterations may help build a more comprehensive model of SZ for diagnosis and treatment.
Supported By: RO1
Keywords: Diffusional Kurtosis Imaging (DKI, Schizophrenia, Gray Matter Microstructure)

T71. Cognitive Mechanisms of Decision Making in Anorexia Nervosa

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Background: Anorexia Nervosa (AN) is characterized by maladaptive food choice behavior, with a mortality rate among the highest of any psychiatric illness. Yet little is known about how AN patients engage in decision processes. Our goal is to elucidate how AN patients make food choices and how these decisions can be subtly "nudged".
Methods: Three independent tasks were administered to healthy controls (HC n=11) and patients with AN (n=9): a food choice, perceptual decision, and cue-approach training (CAT) task. Choices, reaction times and eyetracking measures of eye movements were recorded
Results: Patients placed the highest value on low fat ($t=2.4$, $p=0.02$), low calorie foods compared to HC ($t=1.8$, $p=0.08$). Choice difficulty had a similar effect on choices and reaction times among AN and HC. However, eyetracking data revealed that HCs spent more time viewing higher-valued items, whereas patients with AN did not show this value-modulated gaze bias ($z=7.6$, $p<0.0001$). AN patients show the same preference-choice function as controls, but appear to arrive at these choices by engaging different visual attentional processes. Additionally, both AN (62%, $p=0.04$) and HC participants (62%, $p=0.07$) tended to choose Go over NoGo items following CAT, suggesting that both groups' preferences are similarly malleable.
Conclusions: Maladaptive choices in AN may be characterized by altered visual attentional processes where more equal viewing time is dedicated to both choice options regardless of value. Insight into how food choice behavior can be altered in AN will lead directly to developing better treatments for this dangerous illness.
Supported By: NIH grant R01MH105452 (DS & JS), The Klarman Family Foundation Eating Disorders Research Grant (DS), NSF SPRF grant #1606916 (AB), European Research Council and The Israel Science Foundation (TS), NIH grant R01EY011378 and HHMI (MNS)
Keywords: Anorexia Nervosa, Eye Tracking, Cue-Approach Task

T72. Perinatal High Fat Diet Consumption Alters Circulating Extra-Vesicle mRNA in a Rat Model

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Background: Studies in humans and animal models have suggested the involvement of the neuroendocrine and immune systems in altering offspring brain development under conditions of altered maternal nutrition and metabolic state during gestation. Perinatal maternal high fat diet consumption results in rat offspring with cognitive deficits despite being weaned on a low-fat diet. The finding that extracellular RNA molecules circulate, enter distant cells and alter their phenotype has

transformed our notions of intercellular communication and opened new avenues of investigation for pathogenesis and biomarker studies. We investigated whether extra-vesicular mRNA content was altered in rat dams fed a high fat diet.
Methods: Pregnant Sprague-Dawley rats were divided into 2 dietary groups: 1) standard chow diet (10% kcal fat), and 2) high fat diet (60% kcal fat) beginning on day 2 of gestation and continued through the lactation period. Plasma was collected at the end of lactation and extra-vesicular mRNAs were isolated using the Qiagen exoRNEasy kit. Sequencing libraries were generated using a modified single cell sequencing protocol. Paired-end sequencing was performed and annotation based differential expression was performed using DESeq2.
Results: Our sequencing results found Carbonic Anhydrase 6 (CA6) transcripts to be depleted by 8-fold in dams fed a high fat diet. We validated this finding by quantitative PCR (p-value=0.02).
Conclusions: Our work demonstrates that circulating extra-vesicular mRNA profile in plasma is altered in response to a high fat diet. Currently, we are investigating the functional implications of this finding and CA6's role in in brain development.
Supported By: R21; NIMH
Keywords: Extracellular RNA, RNA-Sequencing, Expression, Diet, Neurodevelopment

T73. Altered Reinforcement Learning From Reward and Punishment in Women With Anorexia Nervosa

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Background: Accumulating evidence suggests anorexia nervosa (AN) is characterized by decreased reward reinforcement learning. Increased punishment sensitivity is also implicated in AN, suggesting that altered learning from both reward and punishment may contribute to maladaptive decision-making and decreased motivation to eat. Since little is known about punishment-based learning in AN, we examined whether AN is associated with altered learning from positive and negative outcomes.
Methods: Women with a current diagnosis of AN (n=41) and control women (CW; n=39) performed a well-validated probabilistic associative learning task that separated learning of stimuli via reward and punishment. Optimal responses were analyzed with a 2 group x 2 learning condition x 4 block repeated measures ANOVA. To examine amount of training, we repeated the ANOVA including a second set of new stimuli.
Results: For Set 1, participants showed robust learning for both reward- and punishment-based trials ($p<0.001$), with greater overall accuracy ($p<0.001$) on punishment trials and greater learning rate ($p<001$) on reward-based trials. AN performed better than CW on reward trials (p=0.003) despite poorer learning rate (p=0.02). When Set 2 was included, a group x set interaction (p=0.002) indicated AN were less accurate than CW on Set 2, particularly for reward trials (p=0.003). AN also performed better on punishment than reward-based trials ($p<0.01$).
Conclusions: Findings suggest both approach and avoidance motivation may influence learning in AN, with deficient reward learning rate and greater punishment learning over time. Given the influence of motivation on learning, distinct treatment strategies based on valence may be useful.
Supported By: R01MH113588
Keywords: Anorexia Nervosa, Reinforcement Learning, Punishment, Reward

T74. Response Bias on the Stop-Signal Task: An Endophenotype of Misophonia?

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Background: Misophonia is a newly defined psychiatric condition in which specific ordinary sounds, such as breathing or lip-smacking, provoke disproportionately strong feelings of irritability, disgust, and anger. To substantiate its classification as a distinct psychiatric disorder and, possibly, as an obsessive-compulsive spectrum disorder (OCSD), we tested whether misophonia, like many OCSDs, is associated with impaired response inhibition.
Methods: We compared behavioral performance on and fMRI responses during a stop-signal task in 22 misophonia patients and 19 healthy controls, matched on age, sex, and education level. Successful and failed stop and correct go trials were contrasted in whole-brain voxel-wise and ROI analyses ($p<0.05$, corrected).
Results: Patients exhibited more time between go and stop stimuli than controls (stop-signal delays; p=0.02), which strongly correlated with inhibition accuracy and reaction times over groups (r=0.90&0.97, $p<0.001$). Patients activated the superior medial frontal gyrus (SMFG) more during inhibition failure, compared to correct going, than controls (p=0.043). Patients lacked inhibition success-related activity in the posterior cingulate cortex (PCC; p=0.014). Whereas left dorsolateral prefrontal cortex (DLPFC) was involved in successful inhibition in controls ($p<0.001$), a trend suggested its involvement in correct going in patients (p=0.073).
Conclusions: While exhibiting intact response inhibition ability, misophonia patients favor accuracy over speed on the stop-signal task. This is associated with neural activity increases in SMFG and decreases in PCC and left DLPFC, which could be related to increased (emotional) self-reflection during inhibition failure, and failure to (correctly) engage areas involved in change detection, and strategic criterion-setting to optimize speed-accuracy trade-off during inhibition success, respectively.
Keywords: Brain Imaging, fMRI, Misophonia, Stop-Signal Task, Response Bias

T75. Amygdala and Ventral Striatum Volume and its Association With Subtypes of Aggression

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Background: Aggressive behavior, as seen in oppositional defiant disorder (ODD) and conduct disorder (CD), has been associated with structural alterations in the amygdala and ventral striatum (VS). However, studies so far have been inconsistent and have not used these measures to differentiate subtypes of aggression. Here we explored the association between volume/shape of the amygdala and VS with reactive (impulsive) and proactive (instrumental) aggression. Callous Unemotional (CU) traits were also taken into account as a continuous measure.
Methods: T1-weighted magnetic resonance images and phenotypic information were collected from 162 children and adolescents with ODD/CD and 92 controls (aged 8-18 years) in a nine-site study. Amygdala and VS volume and shape were determined using the FMRIB integrated registration and segmentation tool. Group comparisons were performed for volume and shape and associations with the different types of aggression were investigated by means of general linear models, correcting for age, sex, IQ, total brain volume and scan-site.
Results: Group differences were found in both VS and amygdala volume, but not shape ($F(1,214)=11.45$, $p<0.001$ and $F(1,214)=8.47$, $p=0.004$ respectively), with smaller volumes in cases versus controls for both structures. In addition, both subcortical volumes were negatively associated with proactive and reactive aggression (p-values <0.01), while only decreased amygdala volume was associated with more CU-traits (coeff=-0.48, $p=0.02$).
Conclusions: Decreased amygdala and VS volume in cases were not specific for reactive and/or proactive subtypes of aggression. However, CU-traits were associated with amygdala volume only, suggesting some overlapping but also unique subcortical alterations related to aggression.
Supported By: EU FP7
Keywords: Aggression, Conduct Disorder, Amygdala Volume, Ventral Striatum, Callous-Unemotional Traits

T76. Involvement of the Endocannabinoid Enzyme Fatty Acid Amide Hydrolase in the Neurobiology of Impulsivity: Positron Emission Tomography Studies With [11C]CURB

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Background: Impulsivity, a major hallmark of addiction and other disorders characterized by the tendency to act without forethought or conscious judgment. Both clinical and preclinical studies have linked trait impulsivity with fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the endogenous cannabinoid, anandamide. Using a novel positron emission tomography (PET) radiotracer for FAAH, [11C]CURB, the present study investigated the relationship between Barratt Impulsiveness scores and FAAH brain levels in healthy individuals.
Methods: FAAH levels in brain were measured using PET imaging with [11C]CURB in 51 healthy volunteers (23 M, 28 F, age= 29 ± 11). Subjects completed the Barratt Impulsiveness scale (BIS-11) and blood samples were collected to determine FAAH C385A genotype (32 C/C, 19 As). Partial linear correlations between FAAH levels (Ik3) and BIS-11 scores were performed with C385A genetics as a covariate.
Results: FAAH levels in the prefrontal cortex ($r = -0.30$, $p = 0.03$), ventral striatum ($r = -0.28$, $p = 0.05$) and whole brain average ($r = -0.33$, $p = 0.02$) showed a significant negative correlation with the BIS-11 factor of self-control. Additionally, FAAH levels in the prefrontal cortex were significantly correlated with the total BIS-11 score ($r = -0.29$, $p = 0.04$).
Conclusions: Our results are in-line with previous neuroimaging studies which provide further evidence for the role of the endocannabinoid system in impulsivity. A better understanding of the neurochemical substrate underlying impulsivity, a risk phenotype involved in addictive and neuropsychiatric disorders may suggest new pharmacotherapies targeting pathological impulsivity in general.
Supported By: NIH, NIDA
Keywords: FAAH, BIS-11, Impulsivity, Endocannabinoids, Anandamide

T77. Automated Reconstruction of White Matter Pathways in Attention-Deficit / Hyperactivity Disorder Using Anatomical Priors

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Background: ADHD has repeatedly been associated with alterations in white matter microstructure, as measured through fractional anisotropy (FA) and acquired through diffusion-weighted MRI (DWI). Due to methodological heterogeneity of analysis techniques, there have been inconsistent results regarding anatomical specificity of changes in FA. The aim of this study was to determine, in an automated manner, whether

FA is related to ADHD in a large cohort of patients and healthy controls.
Methods: A cross-sectional analysis was performed on DWI data collected from 592 adolescents (285 unaffected, 247 affected, 60 subthreshold; mean age = 16.97 years) from the NeuroIMAGE study. Eighteen major white matter pathways in each subject were automatically segmented using TRACULA, a tractography toolbox within Freesurfer. We applied a mixed model regression to test for overall FA differences between groups. To explore tract-specific effects, linear regression was applied for each of the 18 tracts separately.
Results: No significant differences were found for overall, global FA between subject groups. A nominally significant difference in FA between groups was observed in the right corticospinal tract (rCST) [$F(2, 581) = 3.017$; $p = 0.04972$, uncorrected]. No other white matter pathways resulted in a significant difference between groups, and there was no effect of age and gender.
Conclusions: This tractography analysis in a large sample indicates no prominent changes in FA associated with ADHD diagnosis in adolescence. Nevertheless, our results are consistent with previous findings that suggest that FA in the CST is related to changes in hyperactive/impulsive symptoms.
Supported By: Radboudumc Hypatia Grant (R0003664 to Emma Sprooten); NWO Large Investment Grant (1750102007010 to Jan Buitelaar); NWO Brain & Cognition grant (056-13-015 to Jan Buitelaar)
Keywords: ADHD, Diffusion Tensor Imaging (DTI), Tractography, Magnetic Resonance Imaging (MRI), Neuroimaging

T78. Gray Matter Density Alterations in the Dorsolateral Prefrontal Cortex and Anterior Cingulate Cortex Among Veterans With Mild TBI and Depression

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Background: Major depressive disorder (MDD) following mild traumatic brain injury (mTBI) is a common outcome, estimated to occur in up to 50% of cases. Depression is believed to negatively impact functional outcomes for individuals with mTBI. It also significantly increases the chances individuals will struggle with suicidal ideation following injury. It is unclear exactly which areas of the brain may be affected with co-occurring depression and mTBI, however, previous studies have shown that both lesions and stimulation to the bilateral dorsolateral prefrontal cortices and anterior cingulate cortex can impact mood symptoms. We aim to compare gray matter density within the dorsolateral prefrontal cortex and anterior cingulate of Veterans with mTBI between those with (mTBI+MDD) vs. without depression (mTBI-MDD).
Methods: Six Veterans with mTBI completed a neuropsychiatric testing battery for classification of mTBI and mental health disorders. MDD classification was made using the Beck Depression Inventory (Score >20 considered to be diagnostic for MDD). Veterans completed a 3T MRI and a T1-weighted MPRAGE was acquired. Voxel-based morphometry (VBM) analyses using VBM8 for SPM8 was completed.
Results: VBM analyses revealed decreased gray matter density for mTBI+MDD Veterans vs. mTBI-MDD ($p=0.01$, small volume correction) within the left DLPFC (10 voxels) and right DLPFC (2 voxels). VBM analyses also revealed decreased gray matter density for mTBI+MDD vs. mTBI-MDD Veterans ($p=0.01$, small volume correction) within the dorsal ACC (81 voxels).
Conclusions: Veterans with co-occurring mTBI and MDD may have decreased gray matter density in the bilateral DLPFCs and ACC. These findings suggest possible targets for future neuromodulatory treatment.
Supported By: VA RR&D RX00949-01A2 CDA II
Keywords: Mild Traumatic Brain Injury, Major Depression, Volumetric Neuroimaging

T79. Neurodevelopmental Copy Number Variants With Asthma in a Large Pediatric Record Study

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Background: Copy number variants (CNVs) related to neurodevelopmental/mental disorders are common genetic risk factors for autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and schizophrenia. Studies have shown that childhood asthma is a concurrent problem that seems to have some association with psychiatric disorders but the relationship of the two disease categories have not yet been established. This study investigated the clinical penetration of neurodevelopmental CNVs into asthma.
Methods: From previous studies, eight CNVs including NRXN1 del, MYT1L dup, 15q13.3 del/dup, 16p11.2 del/dup, and 22q11.2 del/dup were selected for having some association with neurodevelopmental disorders. Total of 60,644 pediatric subjects aged 0-21 years from the biobank of Center for Applied Genomics (CAG) at Children's Hospital of Philadelphia (CHOP) were screened for the eight selected neurodevelopmental CNVs. Each of the CNV carriers were matched to 5:1 non-carrier control subjects. The analysis for each CNV types was performed using Fisher's Exact Test to compare the two categories using the SAS.
Results: A significant clinical penetrance was found between carriers of the 22q11.2 duplication and frequency of asthma compared to that of the non-carriers ($p=0.048$). The interaction between asthma and mental disorders for 22q11.2 duplication carriers were also found to be significant ($p=0.0128$) compared to that of the non-carriers ($p=0.1047$).
Conclusions: To our knowledge, this is the first report of a CNV association (22q11.2 duplication) for asthma and mental disorders. Clinically, more research should be done in understanding the pathophysiology and the directionality of this genetic association, whether the association is bi-directional or one leads to another.
Keywords: 22q11 Duplication, Asthma, Mental Health

T80. Novel PET Radioligands Show That COX-2, but not COX-1, is Induced by Neuroinflammation in Rhesus Macaque

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Background: The isoenzymes cyclooxygenase 1 (COX-1) and COX-2 play a critical role in mediating inflammation and are primary targets for commonly used nonsteroidal anti-inflammatory drugs (NSAIDs). Our laboratory recently developed two novel PET radioligands for the COX isoenzymes: [11C]PS13 for COX-1 and [11C]MC1 for COX-2. This study evaluated these radioligands in a model of neuroinflammation in rhesus macaques using intracerebral injection of lipopolysaccharide (LPS).
Methods: Four monkeys were injected with LPS in the right putamen. Dynamic brain PET scans were obtained with [11C]PS13 or [11C]MC1 on days 1, 3, and 8 post-injection. To determine specific uptake of the radioligands in brain, blocking scans were performed with either non-radioactive PS13 or MC1 (1 mg/kg). Magnetic resonance imaging (MRI) and [11C]PBR28 positron emission tomography (PET) scans were also obtained post-LPS as positive controls.
Results: Pre-LPS injection, [11C]PS13 showed specific uptake in brain while [11C]MC1 did not. However, post-LPS injection, the distribution volume (VT) of [11C]MC1 increased by 45% while the VT of [11C]PS13 did not change. Post-LPS MRI scans confirmed edema at the injection site, and [11C]PBR28 PET scans showed significantly higher uptake in the ipsilateral putamen. Fluorescent in situ hybridization and immunostaining in post-mortem tissues confirmed the in vivo PET findings.
Conclusions: Our results indicate that COX-2, but not COX-1, is induced after neuroinflammation in rhesus macaque. [11C]PS13 and [11C]MC1 show promise both as biomarkers of COX activity in disorders thought to involve neuroinflammation and as tools to evaluate the delivery and target engagement of NSAIDs.
Supported By: Intramural Research Program of the National Institute of Mental Health, NIH
Keywords: PET imaging, Neuroinflammation, COX-1, COX-2

T81. Regional GABA Concentrations Modulate Inter-Network Resting-State Functional Connectivity

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Background: Coordinated activity within and differential activity between large scale neuronal networks such as the default mode network (DMN) and the control network (CN) is a critical feature of brain organization. The CN usually exhibits activations in response to cognitive tasks while the DMN shows deactivations; in addition, activity between the two networks is anti-correlated at rest. However, how these patterns are generated at the cellular level and derived by neural inhibitoy (GABA) and excitatory (Glu) is not well-understood.
Methods: To address this issue, we used functional MRI to measure whole-brain BOLD signal during resting-state and task-evoked conditions, and MR spectroscopy (MRS) to quantify GABA and glutamate (Glu) concentrations, in nodes within the DMN and CN (MPFC and DLPFC, respectively) in 19 healthy individuals at 3 Tesla.
Results: We found that GABA concentrations in the MPFC were significantly associated with DMN deactivation during a working memory task and with anti-correlation between DMN and CN at rest and during task performance, while GABA concentrations in the DLPFC weakly modulated DMN-CN anti-correlation in the opposite direction. Highlighting specificity, glutamate played a less significant role related to brain activity.
Conclusions: These findings suggest that MPFC and DLPFC GABA activity make differential impacts on task-related activation and inter-network functional connectivity. GABA in the MPFC is involved in orchestrating between-network brain activity at rest and during task performance. Exploring neurochemical characteristics of DMN and CN may provide novel insights into abnormal brain network activity and provide opportunities for developing novel treatment strategies and earlier interventions for neuropsychiatric disorders.
Supported By: NARSAD (F.D.), MH094594 (D.O.), MH104449 (D.O.) and the Intramural Research Program of the National Institute on Drug Abuse of the National Institutes of Health.
Keywords: Anti-correlation, Default Mode Network, GABA, fMRI, Glutamate

T82. Association of Hallucination Sensory Modality to Other Features of Anti-NMDA Receptor Encephalitis

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Background: A majority of patients with anti-NMDA receptor encephalitis (anti-NMDArE) present with signs and symptoms suggesting a primary psychiatric disorder, so are usually first evaluated by a psychiatrist. Hallucinations are common and may contribute to frequent misdiagnosis of this disorder, which delays treatment and greatly increases the risk of serious long-term disability. More information about these hallucinatory symptoms could improve early diagnostic accuracy. Therefore, the aim of this study was to more fully characterize sensory abnormalities in anti-NMDArE.
Methods: PubMed and EMBASE databases were systematically searched for reports of adult cases of anti-NMDArE with behavioral or psychiatric symptoms.
Results: The search identified 230 unique patients (45M, 185F) with mean(S.D.) age 36.5(15.9) and 29.4(10.3) years, respectively ($p < .0005$). Sixty-six (28.7%) patients had fever, 148 (64.3%) had evidence of seizures, and 100 (43.5%) experienced hallucinations. Sensory modalities affected were auditory (20.9%),

visual (12.6%), olfactory (1.3%), taste (.9%), tactile or somatic (.8%), and unspecified (13.9%). Hallucinations on the whole were not associated with fever or seizures (one-tailed Fisher's exact $p > .26$), but auditory ($p = .009$) and visual ($p = .036$) hallucinations were associated with fever. Hallucinations were also associated with greater age ($F[1,228] = 10.72$, $p = .001$). The content of auditory and visual hallucinations was often atypical for a primary psychotic disorder.

Conclusions: Every psychiatrist is likely to encounter patients with anti-NMDArE in the course of his/her career. When accompanied by fever, the presence of hallucinations, especially atypical auditory hallucinations, should prompt active consideration of this diagnosis.

Keywords: NMDA Receptor, Autoimmune Disorder, Hallucinations, Diagnosis

T83. Pannexin-1 Channel Regulates ATP Releasing and Modulates Depressive-Like Behaviors

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Background: Pannexin 1 (Panx1) forms plasma membrane ion channels that are expressed in the brain. Panx1 activation results in the release of nucleotides such as adenosine triphosphate (ATP). Although exogenous ATP has been known to produce a potential antidepressant-like effect, little is known about the role of Panx1 in pathophysiology of depression.

Methods: Pharmacological approaches were used to inhibit pannexin-1 channel function systemically or selectively in the mPFC of the mouse brain. Tests were measured to determine the role of Panx1in behaviors related to anxiety and depression.

Results: Here, we used the chronic social defeat stress (CSDS) model and found a decrease in the expression and function of Panx1 in the medial prefrontal cortex (mPFC) of susceptible mice. Furthermore, pharmacological blockade of Panx1 in the mPFC with carbenoxolone (CBX) (100 mM) or 10Panx (100 μM) was sufficient to induce depressive-like behavior. Finally, systemic and intral-mPFC injection of Mefloquine (a broad-spectrum Panx1 inhibitor, MFQ) both inhibited the activity of Panx1. followed by inducing depressive-like and anxiety behaviors in mice with sub-threshold social defeat stress. Indeed, the behavioral abnormalities induced by MFQ were prevented by preconditioning with ATP in the mPFC.

Conclusions: In summary, with a combination of pharmacological tools and behavioral tests, we have shown that the downregulation of Panx1 in CSDS model results in lacking of extracellular ATP in the mPFC, and then contributes to the depressive-like behaviors. Our findings identify Panx1 channel as a critical ATP-releasing channel that modulates mPFC activity and as a potential risk factor of depression

Keywords: Pannexin-1, ATP, Medial Prefrontal Cortex, Depression, Anxiety

T84. EphB2 in the Amygdala Regulates the Depressive-Like Behaviors Induced by Chronic Social Stress

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Background: Major depressive disorder (MDD) is a widespread psychiatric disorder that results in a substantial personal and economic burden. However, little is known regarding the underlying biology of this disorder. Increasing evidences indicate that the EphB2 receptor has critical role in the psychiatric disorders, such as Alzheimer's disease, pain and anxiety. However, the role and mechanism of EphB2 receptor in the depression are largely uncharacterized.

Methods: We identified EphB2 receptor as a key molecule involved in the modulation of depressive-like behavior in adult mice.

Results: We observed increased EphB2 levels in the amygdala of CSDS mice. Knockdown of EphB2 in the amygdala produced antidepressant-like behavioral effects, and activation of EphB2 in the amygdala induced depressive-like behaviors. The mechanism of EphB2 receptor in the depression involved in the modulation of NMDA receptors. We observed that knockdown of EphB2 in the amygdala rescued the increase of NMDA-mEPSC amplitude and evoked NMDAR-mediated current in the CSDS mice. Knockdown of EphB2 in the amygdala rescued the increase of NMDARs in the CSDS mice.

Conclusions: our results indicate that EphB2 receptor might be a potential target for the treatment of depression.

Keywords: EphB2, Depression, NMDA Receptor

T85. Effect of Deep Brain Stimulation on Inflammatory Markers in Hippocampus of Rodents Exposed to Chronic Unpredictable Stress – a Model of Depression

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Background: Treatment resistant depression (TRD) is a growing public health challenge and deep brain stimulation (DBS) is evolving as a potential therapeutic intervention. While activated immune response is implicated in depression, the ability of DBS in reversing inflammatory changes is unknown.

Methods: Male Wistar rats ($n = 24$) underwent DBS electrode placement in medial forebrain bundle. In a 2X2 design they were assigned to either control or 40 days of chronic unpredictable stress (CUS) group ($n = 12$, each group); half of the animals from each group ($n = 6$) were either stimulated with DBS (DBS-on; 8 hours/day X 7 days) or left unstimulated (DBS-off).

Results: CUS-DBS-off rats showed significant increase in plasma and CSF level of ACTH ($p<0.05$) vs. control DBS-off, control DBS-on, and CUS-DBS-on group. Hippocampi of CUS-DBS-off rats showed significant increase in IL-1beta, IL-5, IL-6, IL-7, interferon-gamma and TNF-alpha ($p<0.05$) vs. control DBS-off and control DBS-on. CUS-DBS-on group showed reversal of some of these changes by significantly reducing levels of IL-1beta, IL-5, and IL-18 ($p<0.05$) but not

IL-6 and IL7 ($p>0.05$). Control DBS-on showed significantly higher and CUS DBS-off showed significantly lower BDNF levels in CSF vs. control DBS-off ($p<0.05$). CUS DBS-on showed significant increase in BDNF levels in CSF vs. CUS DBS-off ($p<0.05$).

Conclusions: These data validate the involvement of immune system in CUS model of depression, and that DBS partially reverses some of these neuroinflammatory and neurotrophic changes.

Supported By: John S. Dunn Foundation

Keywords: Depression, Animal Models, Deep Brain Stimulation, Neuroinflammation

T86. Reduced Functional Connectivity in the Executive Control Network Following Mild Traumatic Brain Injury: Implications for Emotional Regulation

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Background: Emotional disturbances are common following mild traumatic brain injury (mTBI). Recent evidence suggests diffuse damage to large-scale neural networks, such as the executive control network (ECN), may account for these mood changes. The ECN supports a range of domain-general cognitive control functions and play an important role in regulating emotional responses. We hypothesized that ECN functional connectivity (FC) would differ between individuals with mTBI and healthy controls (HCs), and this FC would correlate with aggression.

Methods: Thirty-four individuals (n=17 mTBI, 10 females, age=23.49±3.36 years; n=17 HC, 13 females, age=22.88±5.14 years) completed the Buss-Perry Aggression Questionnaire, which quantifies physical and verbal aggression, anger, hostility, and total aggression. Resting-state FC data were collected. Between-group ROI-to-ROI connectivity in the ECN was calculated using the CONN toolbox, while controlling for age, sex, and depression (FDR-analysis-level corrected at $p<.05$). Partial correlations between connectivity and aggression were calculated.

Results: Adults with mTBI reported significantly elevated levels of physical aggression ($F=12.34$, $p=.001$), anger ($F=12.54$, $p=.001$), and hostility ($F=6.37$, $p=.02$) compared to HCs. In the left ECN, individuals with mTBI exhibited lower FC between the thalamus (xyz=-14, -28, 2) and middle temporal gyrus (MTG; xzy=-59, -42, -12) than HCs ($t=-3.64$, $p=.02$). Thalamic-MTG FC was inversely related to physical aggression ($r=-.50$, $p=.004$) and hostility ($r=-.38$, $p=.03$).

Conclusions: Lower post-mTBI thalamic-MTG FC is associated with increased aggression. As these ECN regions are implicated in voluntary emotion regulation processes, these novel findings indicate mTBI may disrupt large-scale network connections important for regulating anger/aggression.

Supported By: USAMRMC W81XWH-12-0386 awarded to W.D.S. Killgore

Keywords: Mild Traumatic Brain Injury, Aggression, Emotional Regulation, Functional Connectivity, Executive Control

T87. Neural Mediator for the Relation Between Depression Severity and Effortless Emotion Regulation

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Background: It was recently suggested that emotion-regulation (ER) implementation relies on ongoing value tracking by default (on a good-for-me/bad-for-me axis; known to involve vmPFC), while higher-order ER processes, executed in lateral-PFC, can override this default process. As impaired ER and valuation link to core symptoms of depression, we tested an effortless ER process and its utilization of a value-sensitive region in vmPFC in MDD.

Methods: Undergoing fMRI, 103 participants (40 treatment-resistant MDD patients, 63 healthy controls) completed the emotional-stroop task, used to probe for Emotional Conflict Adaptation (ECA; effortless adaptation to consecutive incongruent emotional stimuli), an ER process known to involve vmPFC. A separate monetary reward task localized a value-sensitive region in vmPFC.

We hypothesized that ECA performance will rely on vmPFC recruitment, will involve reduced connectivity with high-order ER regions (lPFC), and that both will be related to depression severity.

Results: vmPFC ROI sensitive to social and monetary value was identified. Across the entire sample (n=103), ECA index positively correlated with vmPFC activation ($p<0.001$). ECA index negatively correlated with vmPFC-rvlFG effective connectivity (gPPI) during ECA trials ($pFWE<0.05$). These results suggest that effortless ER relies on vmPFC activation, and that involvement of a higher-order ER region is concomitant with reduced regulation.

Lastly, ECA index, mediated by vmPFC-rvlPFC task connectivity, significantly accounted for depression severity (CI .0250-.1657).

Conclusions: Our results depict a link between ER, activation in a value-sensitive region in vmPFC and high/low-order ER regions connectivity. Previously unknown, the variance in behavior accounted for by this connectivity pattern, emerged as explanatory of depression symptoms.

Supported By: BSMT Consortium - Chief Scientist Officer (CSO) of the Israeli Ministry of Economy

Keywords: Depression, fMRI, Subjective Value, Emotion Regulation

T88. Reduced Neural Response to Reward in Major Depression Disorder Using a fMRI Reinforcement Learning Task

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Background: Studies have found blunted behavioral reward responsivity in major depressive disorder (MDD) using monetary rewards. However, it is less clear how people with MDD respond to primary rewards and how this is represented at the neural level. In this study, we adjusted a reinforcement learning task to assess the neural response to different reinforcement ratios of primary rewards in MDD participants relative to healthy controls (HC).
Methods: 26 MDD participants and 33 HC participants took part in a three-block event-related learning task during which they had to distinguish between two highly similar stimuli while trying to maximize their intake of taste reward. Unknown to the participants, one stimulus (the target) was associated with more reward outcome, while the other stimulus (non-target) was associated with more neutral outcome. Participants' propensity to incorrectly report a target due to the reward reinforcement was considered a false alarm.
Results: Whole brain analyses showed less BOLD activation in MDD vs. HC participants in the left caudate ($p<.05$, FWE for multiple comparisons) in response to seeing the target vs. non-target, and in the pregenual anterior cingulate cortex ($p<.05$, FWE for multiple comparisons) in response to correctly identifying the target vs. missing the target. However, MDD vs. HC participants showed increased BOLD activation in the OFC/insula ($p<.05$, FWE for multiple comparisons) in response to correctly identifying the target vs. the false alarms.
Conclusions: A better understanding of reward processing, as well as the associated neural pathways, may inform better treatments for depression.
Supported By: Medical Research Center PhD Scholarship scheme
Keywords: Depression, Reward, Reinforcement Learning

T89. Group II Metabotropic Glutamate Receptor Blockade Promotes Stress Resilience

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Background: Stress is one of the most widely recognized and well-studied risk factors for the development of psychiatric disorders, including depression. Enhancing stress resilience may be a therapeutic strategy to prevent the development of depression, or the exacerbation of symptoms. Group II metabotropic glutamate receptor (mGluR2 and mGluR3) antagonists have gained attention for their rapid-acting antidepressant action in animal models; however, the effects of modulating these receptors on stress resilience have not been studied as extensively.
Methods: We assessed the effects of pretreatment with the selective group II antagonist LY341495 or agonist LY379268 on stress resilience in the learned helplessness (LH) paradigm. To assess subtype-specific effects, we evaluated the effects of stress on knockout mice lacking either mGluR2 (Grm2-/-) or mGluR3 (Grm3-/) in the forced-swim test (FST), LH paradigm, chronic social defeat stress (CSDS) paradigm, and stress-induced hyperthermia (SIH) test.
Results: Treatment with LY341495 prior to exposure to inescapable shock decreased the development of helpless behavior in the LH paradigm. In contrast, treatment with the group II mGluR agonist LY379268 increased development of helplessness in the same paradigm. Furthermore, we show that Grm2-/-, but not Grm3-/-, mice are more resilient to stress in the FST, LH and CSDS paradigms, and SIH test, as compared to wild-type controls.
Conclusions: Using both pharmacological and genetic manipulations, our results demonstrate that activation of group II mGluR receptors promotes stress susceptibility, while inhibition of mGluR2 prevents such effects. These data suggest that mGluR2 antagonists may be protective against stress-induced changes which underlie susceptibility depression.
Supported By: NIH grant MH107615 to TDG; T32 GM008181 Training Program in Integrative Membrane Biology NIH/NIGMS
Keywords: Major Depression, Stress, Prevention, Metabotropic Glutamate Receptors, Novel Treatments

T90. A Conceptual and Metanalytic Review of Reward Processing in the Pathogenesis of Depression

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Background: Reward processing encompasses multiple processes related to valuation of objects and approach/avoidance behaviors towards such objects. These processes are implicated in depression and anhedonia in particular. Yet, several questions concerning the causal contribution of reward processing remain unanswered. Here we combine conceptual and quantitative findings across fMRI and EEG methodologies.
Methods: Forty-four articles of 58401 surveyed met inclusion criteria for an fMRI (32) and EEG (12) meta-analysis, respectively. fMRI studies focused on reward anticipation and feedback. EEG studies investigated the Feedback Related Negativity (FRN) event-related potential. To test the association with depression, we applied Activation Likelihood Estimation (ALE) to the fMRI data, and random effects meta-analysis to the EEG data. A list of longitudinal studies was also examined.
Results: In fMRI, we found significantly reduced striatal activation in individuals with depression during reward feedback in whole brain analyses. In region of interest analyses, there was also reduced activation in reward anticipation, especially in those under age 18. The FRN was also significantly blunted in depression, particularly under 18-year olds. Longitudinal studies showed that reduced striatal activation in fMRI and blunted FRN in EEG preceded the onset of depression in adolescents.
Conclusions: We find consistent neural abnormalities during reward feedback in depression in the form of reduced striatal and FRN signals appearing before the onset of depression and

therefore probably contributing to the pathogenesis of depression. We map these abnormalities on current concepts of reward processing and discuss current gaps in the literature, such as intervention designs to probe those mechanisms.
Supported By: NIMH Intramural Research Program
Keywords: Depression, Reward, Meta-analysis, fMRI, EEG

T91. Impairments in Resting State Connectivity are Associated With Cannabis Use and Major Depressive Disorder

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Background: Little is known about the effect of marijuana (MJ) use in people with major depressive disorder (MDD). This is particularly concerning because both MJ use and MDD are independently associated with similar psychological, cognitive and neural impairments. This study examined the effect of MDD and marijuana use on resting-state connectivity in the default-mode network (DMN), the salience network (SN), and the central executive network (CEN).
Methods: We completed resting state scans on 81 participants between the ages 18-25 years, consisting of four groups: control participants (CON) with neither MDD nor MJ use, control participants with MJ use (MJ), MDD participants without MJ use (MDD), and MDD participants with MJ use (MDD+MJ). Depressive and anxiety symptoms were assessed using the Mood and Anxiety Symptom Questionnaire and a clinical interview for diagnosis (SCID). Resting state networks were extracted using Melodic's independent component analysis in FSL.
Results: We found that MDD had increased resting state activity compared with all other groups in the anterior DMN (aDMN), the salience network, and CEN. MDD also showed greater activity compared to CON and MJ in the posterior DMN (pDMN). MDD+MJ had increased activation in the pDMN compared to MJ without MDD. There was a significant correlation for age of marijuana use onset and the aDMN ($r=0.36$, $p=0.023$) and CEN ($r=0.42$, $p=0.008$). Anxiety symptoms correlated with connectivity in the pDMN ($r=0.33$, $p=0.041$).
Conclusions: Results suggest that cannabis use and symptoms of major depressive disorder are associated with differences in resting state connectivity, with depression having the largest effect across networks.
Supported By: NIDA K01 DA034093, NIDA T32DA015036, P41EB015896, S10RR023043, S10RR023401
Keywords: Resting State fMRI, Major Depressive Disorder (MDD), Cannabis, Default Mode Network, Salience Network

T92. Time Scales of Encoding the Reward Prediction Error in Youth: Representation of Past Events

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Background: Reward Prediction Error (RPE), the difference between the outcome and the predicted value, is integral to reinforcement learning, used by organisms to maximize wins and minimize losses. Aberrations in RPE signals are thought to underlie common psychiatric disorders such as depression, where behavior is not modified efficiently relative to environmental cues. Here, we test a fundamental property of RPE encoding, namely how it is influenced by previous outcomes.
Methods: Young healthy subjects (10.61 ± 0.3 years), completed the reward task piñata. RPE encoding was compared across different RPE calculation models, considering either the previous 5, 10, 15, 20 or all trials outcomes. To analyze the respective brain signals, these RPEs were used to parametrically modulate fMRI BOLD activation.
Results: Positive RPE encoding in the striatum does not depend on the chosen model, and whether more than the recent 5 outcomes are considered ($p>0.5$, $<10\%$ change in cluster size). Whereas, negative RPE signals in the insula seem to increase as more previous trial outcomes are considered ($>200\%$ increase in cluster size from 5 to 20 last outcomes).
Conclusions: Considering a longer time window for previous outcomes, may improve the prediction value estimation for negative RPE signals, suggesting a longer memory of previous events. Whereas, positive RPE signals do not appear to be affected by the chosen RPE model, hence these signals are mostly impacted by recent outcomes. This characterization increases our understanding of encoding RPE value in the brain, and the time scale for previous events to affect our expectation and behavior, in health or psychopathology.
Supported By: National Institutes of Health Intramural Research Program
Keywords: Reward Prediction, Monetary Loss, Striatum, Insula, Brain Imaging, fMRI

T93. Neurobiology of Processing Emotional Prosody in Unipolar Depression

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Background: Major depressive disorder (MDD) is characterized by a biased emotion perception. In the auditory domain, MDD patients have been shown to exhibit attenuated processing of positive emotions expressed by speech melody (i.e. prosody). So far, no neuroimaging studies examining the neural basis of altered processing of emotional prosody in MDD are available.
Methods: In the current study, we addressed this issue by examining the emotion bias in MDD during the evaluation of happy, neutral, and angry prosodic stimuli on a five-point Likert scale during functional magnetic resonance imaging (fMRI) in 30 MDD patients and 30 healthy controls (HC).
Results: As expected, MDD patients rated happy prosody less intense than healthy controls (HC). At neural level, stronger activation in the middle superior temporal gyrus (STG) and the amygdala was found in all participants when processing emotional as compared to neutral prosody. MDD patients exhibited an increased activation of the amygdala during

processing prosody irrespective of valence while no significant differences between groups were found for the STG, indicating that altered processing of prosodic emotions in MDD occurs rather at the subcortical than cortical level. Concurring with the valence-specific behavioral effect of attenuated evaluation of positive prosodic stimuli, activation within the left amygdala of MDD patients correlated with ratings of happy, but not neutral or angry prosody.
Conclusions: Our study provides first insights in the neural basis of reduced experience of positive information and an abnormally increased amygdala activity during prosody processing.
Supported By: Deutsche Forschungsgemeinschaft (DFG)
Keywords: Depression, Emotion Processing, Prosody, fMRI, Amygdala

T94. Intrinsic Organization of the Salience Network While Processing Incentive Motivation and its Influence on Motivational Behavior

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Background: Incentive motivation is known to be largely influenced by reinforcement's saliency. However, the contribution of the known intrinsic salience network to incentive processing was not studied at the network-level, nor was its contribution to modulation of motivational behavior.

We aimed to investigate whether there was a difference in hierarchy and organization of the intrinsic salience-network during motivational task vs. resting-state, further inspecting the relations of network hierarchy to motivational behavior.
Methods: 43 subjects underwent fMRI while performing a motivational task manipulating high and low goal-conflict, and a 5-minutes resting-state scan.

To compare the intrinsic organization of the salience network we employed Dependency Network Analysis (DepNA), enabling the evaluation of a network's hierarchy by assessing the influence of predefined nodes.
Results: A general increase in connectivity within the salience network during task vs. rest was found. Specifically, the medio-dorsal thalamus (mdThal), anterior insula, SMA, dorsal striatum and PAG were significantly more influencing on- and more influenced by- other nodes of the network during task.

Importantly, higher influencing degree of the mdThal, PAG and SMA was related to less approach behavior preformed during the task under high goal-conflict, suggesting that increased connectivity within the salience-network reduces the tendency to employ risky approach behavior.
Conclusions: The mdThal and SMA were previously related to action-outcome contingencies and transformation of reinforcing values to motor responses, while the PAG is a known node of the flight-fight-freeze system. Further investigations should consider these regions as potential target-specific interventions for psychiatric conditions involving diminished approach behavior, such as depression and anxiety.
Keywords: Incentive Motivation, Salience Network, Brain Imaging, fMRI, Dependency Network Analysis (DepNA), Approach/Avoidance

T95. Functional Characterization of a DGKH Genetic Risk Variant for Bipolar Disorder in a Cell Model

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Background: To investigate the role of a previously described DGKH (diaacylglycerol kinase eta gene) genetic risk variant in the ethiopathogenesis of bipolar disorder (rs994856/rs9525580/rs9525584 GAT haplotyp) cells models were generated from healthy controls and bipolar patients with and without the DGKH risk haplotype.
Methods: Induced pluripotent stem cell lines (IPS) were generated from primary fibroblasts. IPS cell lines were tested positive for pluripotency (PCR, immunostaining, embryoid body assay, molecular karyotyping). IPS cells were differentiated in NPCs and dopaminergic neurons. Expression and activity of DGKη and PKCδ in fibroblasts was investigated by western-blot and IP kinase activity assay and the influence of triamcinolonacetonid (TAA) as a model of stress was investigated.
Results: Bona fide human iPS cell lines could be generated from bipolar patients and healthy controls with and without risk haplotype (each n=1). IPS cell lines were then successfully differentiated in NPCs and TH-positive dopaminergic neuronal cells. In the fibroblast cells, DGKη expression and activity was higher in the bipolar cells compared to healthy controls independent from the risk haplotype. TAA influence was higher on bipolar than control cells.
Conclusions: We could generate a neuronal cell model of a risk gene variant associated with bipolar disorder. Experiments on the fibroblast cells of the same patients and controls suggest a difference in DGKη protein expression and enzyme activity between bipolar patients and healthy controls independent from this risk genotype which is in contrast to previous gene expression studies. However, the results confirm the role of DGKη in the molecular pathomechanims of bipolar disorder.
Supported By: Young researcher grant from the University Hospital of Frankfurt, Frankfurt/Main, Germany
Keywords: Bipolar Disorder, Induced Pluripotent Stem Cell, Genetic Variants, Induced Neuronal Cells, Affective Disorders

T96. Cortical Astroglial-Mediated Plasticity in Chronic Stress

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Background: Recent studies have suggested that cortical astroglia play an important role in depressive-like behaviors. Potential astroglial contributions have been proposed based on their neuroplastic functions such as glutamate recycling

and synaptic plasticity. However, the specific mechanisms by which astroglial cells contribute or protect against a depressive phenotype remain unknown.
Methods: To delineate astroglial changes that accompany depressive-like behavior, we used transgenic mice (AldHL1-L10-GFP) exposed to chronic variable stress (CVS) and profiled the astroglial translatome using translating ribosome affinity purification (TRAP) in conjunction with RNAseq.
Results: As expected, CVS significantly increased anxiety and depressive-like behaviours, corticosterone levels and decreased GFAP expression in astroglia, although this did not reflect a change in the total number of astroglial cells. TRAP-seq results showed that CVS decreased genes associated with astroglial plasticity: RhoGTPases, growth factor signaling, and transcription regulation, together with an increase in genes associated with the formation of extra-cellular matrices such as peri-neuronal nets (PNNs). PNNs inhibit neuroplasticity and astroglia contribute to the formation, organization and maintenance of PNNs. To validate our findings and elucidate the role of PNNs in recovery from chronic stress, we degraded PNNs in the prefrontal cortex of mice exposed to CVS which reversed the depressive phenotype.
Conclusions: These studies suggest an overall decrease in cortical astroglial plasticity following CVS and support a neuroplasticity hypothesis of depressive behaviors in which astroglia play an important role.
Keywords: Chronic Stress, Astrocytes, Plasticity, Cortex, Transcriptome

T97. Neural Underpinnings of the Hedonic Effects of Gamma-Hydroxybutyrate in Humans

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Background: Gamma-hydroxybutyrate (GHB) is an endogenous neuromodulator that stimulates GHB- and GABA-B receptors. It is clinically used for the treatment of neuropsychiatric disorders such as narcolepsy, alcohol withdrawal, and fibromyalgia, but also instrumentalized illicitly for recreational purposes. We aimed to investigate potential hedonic GHB effects and the underlying neural mechanisms.
Methods: We used a placebo-controlled, double-blind, randomized, cross-over functional magnetic resonance imaging (fMRI) design, and assessed the effects of GHB (35 mg/kg p.o.) in 19 healthy male volunteers on regional cerebral blood flow (rCBF), resting-state functional connectivity (rsFC), and subjective hedonic effects using visual analog scales.
Results: GHB increased subjective ratings for emotion and body awareness, stimulation, euphoria, and sexual arousal ($p<.01$-001, Bonferroni-corrected). The drug increased rCBF in the right anterior insula (rAI) and the bilateral anterior cingulate cortex (ACC) and rsFC of the salience network to the central executive network. Moreover, GHB increased rAI-rsFC to the right thalamus and the bilateral superior frontal gyrus, and decreased ACC-rsFC to the bilateral paracentral lobule (all $p<.05$, cluster-corrected). Exploratory correlations were as follows (all $p<.05$, uncorrected): body and emotion awareness with rAI and ACC rCBF, stimulation with rsFC to the central executive network, and euphoria with increased rAI-rsFC to bilateral superior frontal gyrus.
Conclusions: GHB induces hedonic subjective effects and modulates limbic rCBF and rsFC with areas that are linked to regulation of mood, cognitive control, and sexual arousal. This offers models for the drug's unique effects in neuropsychiatric disorders and for hedonic instrumentalization, as well as perspectives for further investigations in affective disorders.
Supported By: Prof. Dr. Erich Seifritz
Keywords: Sodium Oxybate, Anhedonia, Liquid Ecstasy, Depression

T98. Electrical Stimulation Rescues Dopaminergic Neurodegeneration in the Dorsal Raphe Nucleus of Vulnerable Depressive-Like Rats

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Background: Electrical stimulation has been proposed as a potential therapy for patients with treatment-resistant depression. In this study, we investigate the effects of high-frequency stimulation (HFS) in different brain regions on various depressive-like behaviors using the stress resilience and vulnerable rat depression models.
Methods: Animals were exposed to chronic unpredictable stress procedures (CUS) for 3 weeks. Vulnerable and resilience animals were characterized based on their sucrose consumption levels during CUS procedures. CUS-treated rats received HFS in the lateral habenula (LHb), ventromedial prefrontal cortex (vmPFC), nucleus accumbens (NAc) and they were tested for depressive-like behavioral experiments. The morphological changes of dopaminergic neuron were determined by immunohistochemical labeling methods as well as biochemical approaches.
Results: CUS exposure for 3 weeks increased number of animals (51%) exhibiting reduced sucrose consumption, separating the resilience and vulnerable group of CUS-induced model. Interestingly, vmPFC HFS significantly reduced anxiety response, increased hedonia and motivation levels for food intake in the vulnerable group compared to the resilience group, while HFS in other brain regions did not show difference. HFS in vmPFC and LHb also showed reduced behavioral despair in both CUS vulnerable and resilience group. In histochemistry, our results demonstrate that vmPFC HFS rescued the stress-induced dopamine neuron degeneration in the dorsal raphe nucleus.
Conclusions: These results suggest that vmPFC HFS effectively restores depressive-like behaviors by mechanisms of dorsal raphe dopaminergic neurons restoration in the vulnerable CUS-induced model. Further studies are needed to understand the underlying mechanisms of HFS on the resilience and vulnerable group of CUS-induced depression models
Keywords: High-Frequency Stimulation, Depressive-like Behavior, Resilience and Vulnerable, Dopamine, Dorsal Raphe Nucleus

T99. Inter-Relationship Between Consequences of Mild Brain Mitochondrial-Dysfunction and Agents That Promote Mitochondrial Respiration

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Background: Mitochondrial-function is crucial for synaptic-plasticity and cellular-resilience. Involvement of brain mitochondrial-dysfunction/elevated ROS levels and attenuated autophagy are implicated in neuropsychiatric-disorders. We aimed to model mild mitochondrial-dysfunction assumed in bipolar-disorder by exposing human neuronal cells to rotenone and find out whether ROS-scavengers and/or autophagy enhancers can ameliorate neuronal mild mitochondrial-dysfunction.
Methods: SHSY5Y cells were incubated with an extremely low rotenone dose (mitochondrial complex-I inhibitor, 10 pM) for 72 and 96 hours. Mitochondrial parameters (e.g. oxygen-consumption-rate and membrane-potential) were monitored using the Seahorse and Operreta apparatuses and specific kits.
Results: 10 pM rotenone did not affect cell-viability but induced a dual effect on mitochondrial-respiration: 72 hours exposure induced an overshooting increased basal, maximal and ATP-linked oxygen-consumption-rate; 96 hours significantly decreased all OCR parameters. The autophagy enhancers trehalose, rapamycin and resveratrol added for the last 24 of the 72 hours of rotenone counteracted rotenone`s effect; lithium for the last 48 of the 96 hours reversed rotenone's effect.
Conclusions: The effect of 10 pM rotenone mimics bipolar-disorder studies in which neuronal cell death is not discerned despite reproducible reports of mitochondrial-dysfunction. The enhancing effect of the low dose of rotenone on mitochondrial-respiration parameters is interpretable as the cells' compensatory response to the very mild mitochondrial-dysfunction. Our regime differs from the rotenone-induced Parkinson's model by not affecting ROS levels nor cell viability but reducing most OCR parameters following 96 hours of exposure. The effect of lithium reversing rotenone's effect on OCR parameters is compatible with lithium's known positive effects on mitochondrial-function, in general, and oxidative phosphorylation complexes, in particular.
Supported By: Israel Science Foundation
Keywords: Rotenone, Mitochondrial-Dysfunction, Autophagy

T100. Linking GABAergic, Astroglial and Synaptic Dysfunctions to Stress-Induced Depressive-Like Endophenotype: Importance of Astroglial Integrity

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Background: Major depressive disorder (MDD) is a severe heterogeneous mental condition affecting multiple cell-specific pathways. Molecular changes within GABA cells, astrocytes and synapses in the prefrontal cortex (PFC) are reported in MDD and stress-based rodent models. This study aims to identify the sequence of events affecting these compartments i.e. the onset and trajectory of the stress-induced cell-specific changes and their correlation with behavior.
Methods: Using the chronic restraint stress (CRS) paradigm (1h restraint stress, 2x day) in male and female mice, we examined CRS effects on anxiety- and anhedonia-like behaviors and on expression of GABAergic, astrocytic and synaptic markers in the PFC at different time points (1 to 5 weeks, n=16/group).
Results: CRS induced anxiety-like behavior regardless of the CRS duration but showed a progressive increase in anhedonia-like behavior after the 3rd week of CRS. At the cellular level, GABAergic marker expression (GAD67 and vGAT) reductions were identified as early as the first week of CRS. Astrocytic marker (GFAP, GS, GLT1) expression levels were altered after 3 weeks of CRS and preceded a decrease in synaptic (PSD-95, Syn1) markers. Interestingly, while anxiety-like behaviors correlated with GABAergic marker expression, astrocytic marker expression profile correlated with both anhedonia- and anxiety-like deficits, suggesting that astroglial dysfunction coincides with the emergence of the maladaptive response to stress.
Conclusions: Chronic stress-induced time-dependent cell-specific alterations are linked to various behavioral outcomes. Our results suggest that astroglial dysfunction may be a turning-point in stress response leading to the pathological state associated with MDD and other stress-related illnesses.
Supported By: NARSAD; CAMH.
Keywords: Depression, Chronic Stress, GABA, Astrocytes, Behavior

T101. Accelerated Maturation Phenotypes in Patient-Derived Cell Models of Bipolar Disorder

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Background: Bipolar disorder (BP) is a complex neuropsychiatric disorder associated with episodes of altered mood, energy, and sleep. The molecular and cellular mechanisms of BP are poorly understood. Patient-derived induced pluripotent stem cells (iPSC) provide a model for studying neurodevelopment in BP, which may help uncover disease mechanisms.
Methods: We derived iPSC from fibroblasts from neurotypical controls (C) and BP patients, and differentiated them into neurons and astrocytes. We studied neuronal maturation by measuring developmental gene expression as well as electrophysiology. Using fluorescent calcium indicators, we measured spontaneous and activity-evoked calcium transients in BP and C neurons. We also examined ATP-evoked calcium signals in immature and CNTF-matured astrocytes from BP and C subjects.
Results: Immunofluorescence and electrophysiological data suggest that BP neurons matured more quickly and lost

progenitor markers at earlier developmental ages than C neurons. BP neurons displayed larger calcium signals in response to chemical stimulation than C neurons. By contrast, in a field depolarization paradigm, BP neurons had smaller calcium signals than C neurons. CNTF maturation altered calcium signaling differentially between BP and C astrocytes.
Conclusions: Our data suggest that cells derived from BP patients may mature more quickly than C cells, and support the hypothesis that BP is a neurodevelopmental disorder. Future studies will seek to identify the signaling pathways involved in maturational differences between BP and C cells, and determine whether maturation in BP cells can be corrected to match C patterns.
Supported By: NIMH U19MH106434; NCATS KL2TR002241; NCATS UL1TR002240; Heinz C. Prechter Bipolar Research Program; Steven M Schwartzberg Memorial Fund; Richard Tam Foundation
Keywords: Pluripotent Stem Cells, Calcium Signaling, Neurodevelopment, Bipolar Disorder

T102. Plasma Interleukin 1 Beta Positively Correlates With Anxiety Scores in Youths With Bipolar Disorder

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Background: Bipolar Spectrum Disorders (BSD) and Anxiety Disorders are highly comorbid. Furthermore, school avoidance behavior can be a presenting symptom in youths with underlying anxiety. Immune dysfunction has been implicated in the pathophysiology of bipolar disorder but the role of immune markers such a proinflammatory cytokines in youths with bipolar disorder has not been adequately studied. We aimed to examine the association of the pro-inflammatory cytokine, IL-1β with anxiety symptoms and school avoidance behavior in youths with BSD.
Methods: 16 youths with BSD (7-17 years inclusive, diagnosed with the MINI– KID Client version 7.0 for the youth) were recruited. The MINI – KID 7.0 Parent version was used to interview parents about their child's diagnoses. Youth were also administered the SCARED-C (Screen for Childhood Anxiety Related Disorders – Child Version) questionnaire. IL-1β was measured in fasting plasma using ELISA. Spearman's Rho test was performed to evaluate the relationship between IL-1β and the anxiety measures.
Results: IL-1β positively correlated with SCARED-C SH School Avoidance subscale (ρ=0.53, p=0.037) and there was a trend towards positive correlation with the SCARED-c GD: Generalized Anxiety subscale (ρ =-0.49, p=0.052).
Conclusions: If our preliminary results are replicated in future longitudinal studies, then IL-1β might become a biomarker of anxiety-related features in youths with BSD.
Supported By: The John S Dunn Foundation
Keywords: Anxiety, Mood Disorders, Bipolar Disorder, Metabolomics, Biomarkers

T103. Transcriptome Alterations for Posttraumatic Stress Disorder in Human Prefrontal Cortex

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Background: Posttraumatic stress disorder (PTSD) is a chronic and debilitating disease that can occur after a severe traumatic event in certain individual. Current evidence from peripheral blood studies demonstrates the occurrence of transcriptional aberrations in PTSD patients, but there have been few studies of brains of PTSD subjects.
Methods: RNA-sequencing was performed on mRNA of subgenual PFC of 61 PTSD, 48 MDD, and 47 control subjects. Pairwise differential expression analysis was performed with Cuffdiff using the negative binomial distribution and a nominal significance threshold of $p<0.05$ and fold change (FC) >1.3. Enrichment of gene ontology, network building, upstream and hub gene identification were performed using Ingenuity Pathway Analysis.
Results: Hierarchical clustering of differentially expressed genes (DEG) indicated PTSD and MDD cohorts clustered more closely together than either with the control cohort. 276 DEG were identified between PTSD and control subjects. There were 304 DEGs between MDD and the control subjects. Of these comparisons, 67 genes were found to be similarly regulated between PTSD and MDD. 189 DEGs were found between MDD and PTSD cohorts. We identified a PTSD specific gene network that has significant overlap with glucocorticoid signaling pathways. Differentially expressed genes were assessed through Fisher's exact test corrected for multiple testing (Benjamini-Hochberg, FDR 0.1).
Conclusions: Overall, our work demonstrates novel convergent evidence for biological networks related to PTSD and glucocorticoid signaling which may prove fundamentally important for understanding the neurobiology and treatment of PTSD.
Supported By: VA National Center for PTSD
Keywords: Transcriptome, PTSD - Posttraumatic Stress Disorder, RNA-sequencing, Human Postmortem Brain

T104. Plasma Interleukin-1 Beta is Associated With Deficits in Spatial Recognition Memory in Youth With Bipolar Spectrum Disorders

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Background: Deficits in youth with Bipolar Spectrum Disorders (BSD) include chronic emotion dysregulation, affect recognition, cognitive decline and sensorimotor deficits. Dysregulated levels of cytokines, associated with BSD pathophysiology, have also been associated with cognitive deficits including impaired spatial recognition memory (SRM) in individuals with BSD. This study is an evaluation of the association between the proinflammatory cytokine interleukin-1 beta (IL-1β) and SRM in youths with BSD.
Methods: 16 youths with BSD (7-17 years inclusive, diagnosed with Mini − KID Client version 7.0 for the youth) were recruited from an outpatient pediatric bipolar disorders specialty clinic at an academic institution. The MINI − KID 7.0 Parent version was used to interview parents about their child's diagnoses. All the participants underwent cognitive testing (including SRM) using the CANTAB neurocognitive test battery. ELISA (performed on fasting plasma) was used to measure IL-1β levels. Spearman's Rho was used to evaluate the correlation between IL-1β and scores on the SRM.
Results: IL-1β levels negatively correlated with SRM (percent correct) scores on CANTAB ($r=-0.57$, $p=0.041$) in this sample of youths with BSD.
Conclusions: These preliminary results from our ongoing study demonstrate a probable association of IL-1β, an inflammatory cytokine, with deficits in spatial recognition memory in youths with BSD. Further studies in larger, prospective cohorts are required to further establish this association.
Supported By: The John S. Dunn Foundation
Keywords: Biomarkers, Proteomics, Bipolar Disorder, Youth, Inflammatory Cytokines

T105. Changes of TSPO Affects Selective Removal of Mitochondria via Mitophagy

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Background: Bipolar disorder (BD) is a chronic, debilitating illness with a global prevalence of up to 4.8%. Accumulated evidences suggest that mitochondrial deficit is implicated in BD and TSPO plays an important role in regulating mitochondrial function, including the mitophagy pathway. Thus, we aimed to investigate the protein levels of TSPO and mitophagy pathway in peripheral blood mononuclear cells (PBMCs) from BD-I patients and healthy controls.
Methods: 20 patients with BD-I and 20 age- and sex-matched healthy controls were enrolled for this study. PBMCs were separated using LeucoPREP brand cell separation tubes and the TSPO and mitophagy-related pathway were interrogated by PCR and Western Blotting.
Results: Our results showed an up-regulation of the TSPO pathway proteins (TSPO and VDAC) and a significantly down-regulation of the mitophagy pathway proteins (Parkin, p62 and LC3B), both in terms of gene expression and protein levels in PBMCs from BD-I patients. Moreover, we demonstrate that the ratio of TSPO to VDAC1 is higher in BD-I. Additionally, we found a negative correlation between Parkin mRNA levels and TSPO protein levels, as well as a positive correlation between TSPO and VDCA. Also, a negative correlation was found between TSPO and LC3, while a positive correlation was found between Parkin and LC3.
Conclusions: The data reported here suggest that TSPO interacts with VDAC, and inhibits mitochondrial autophagy leading to an accumulation of dysfunctional mitochondria, altering the appearance of the network. Finally, our findings in PBMCs of patients with BD support a link between mitochondrial dysfunction and the pathophysiology of BD.
Keywords: Bipolar Disorder, Mitochondria, Mitophagy, Peripheral Blood Mononuclear Cells, TSPO

T106. Ethanol and Lithium Normalize Glutamate-Induced Elevation of Intracellular Sodium in Olfactory Neuroepithelial Cells of Bipolar Subjects, but not Non-Bipolar Controls: Evidence for Self-Medication Hypothesis

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Background: Alcoholism is highly prevalent in individuals diagnosed with bipolar disorder (BD). The nature of the association between alcoholism and bipolar disorder is not well understood. In the current study olfactory neuroepithelial progenitor cells (ONP) obtained from patients with BD and non-BD subjects were used to examine this relationship.
Methods: Three ONP cell lines from BD, and three gender and age matched non-bipolar cell lines were used. ONP cultured in MEM, gentamycin 0.1mg/mL, and FBS 10%, in 5% CO2. 0.1 M glutamate will increase the intracellular sodium ([Na]in) levels two times, was used to model "mania" in the cells. The treatments were modeled with 0.05 M ethanol and 1mM lithium.
Results: Treatment with either ethanol or MSG alone for 6 hours increased intracellular [Na]in in both BD ($2.3 \pm$ SD 0.62 and 2.1 ± 0.18, respectively) and non-BD subjects (2.19 ± 1.4 and 2.97 ± 2.2, respectively). Both lithium and ethanol lowered the elevation of [Na]in by glutamate in BD only (0.65 ± 0.07 and 0.7 ± 0.28, respectively, $P < 0.05$), not non-BD cells (2.42 ± 1.1 and 1.7 ± 0.76, respectively).
Conclusions: Both lithium and ethanol normalize glutamate -induced elevation of [Na]in in cells obtained from subjects with BD only. Neither is effective in countering the effect of glutamate on [Na]in in cells from non-BD. This first biological evidence of "self-medication" hypothesis may indeed have biological underpinnings.
Keywords: Bipolar Disorder, Ethanol, Intracellular Sodium, Olfactory Neuroepithelial, Progenitor Cell

T107. Membrane Potential of Differentiated Olfactory Neuroepithelial Progenitors Derived From Bipolar and Non-Bipolar Subjects

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Background: Disturbed ion homeostasis involved in bipolar illness. The aim of this study is to test the membrane potential in olfactory neuroepithelial progenitors cells (ONPs) derived from bipolar and non-bipolar subjects.
Methods: ONPs were biopsied from gender and age matched bipolar and non-bipolar subjects. Three bipolar and six non-bipolar cell lines were used. ONPs were grown in MEM, gentamicin 0.1 mg/mL and FBS 10%, with 5% CO2. Differentiation was achieved by treating ONPs for 4 days with retinoic acid (1 μM) and forskolin (5 μM), followed by 3 days in which the forskolin is replaced with sonic hedgehog (15 nM) in DMEM with 1% B27 and 0.5% N2. Immunocytochemistry for the neuronal marker (NeuN) and glial marker (GFAP and MBP) were used to determine cell type. Membrane potential was measured by path-clamp.
Results: ONPs are heterogeneous. Small cells, with diameters around 15 microns, had resting membrane potentials (RMPs) around -20mV. Larger cells, with diameters are around 25 microns, have had RMPs around -45 mV. Immunocytochemistry showed the large cells are GFAP and MBP positive cells. Larger cells were used to measure capacitance, RMPs, action potential (AP) peak, action potential (AP) overshoot, action potential (AP) threshold. The lower AP peak in ONPs from bipolar subjects compare to non-bipolar subjects (66.33±6.85 vs 89.36±1.88 mV, $p=0.03$). There is no difference on capacitance, RMPs, AP overshoot and AP threshold.
Conclusions: ONPs deprived from bipolar subjects has lower AP peak compared to non-bipolar ONPs. The significance of these findings needs to be investigated.
Keywords: Olfactory Neuroepithelial Progenitors Cell, Bipolar Disorder, Membrane Potential

T108. AMPA Receptor Subunit Expression and Receptor Binding in Patients With Major Depressive Disorder: A Systematic Review of Postmortem Studies

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Background: While altered trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors has been reported in major depressive disorder (MDD), the findings widely differ among studies. In this systematic review, we examined published data from postmortem studies that investigated the AMPA receptor expression in MDD.
Methods: We conducted a systematic literature search for postmortem studies examining the expression of AMPA receptor subunits or receptor binding in patients with MDD compared to healthy individuals in November 2017, using PubMed, Medline and Embase. Cross-reference and hand searches were also performed.
Results: Nine relevant articles were identified; they consisted of 13 studies that examined AMPA receptor subunit (or related molecule) transcript or protein expression, or AMPA receptor binding levels. The most frequently investigated region was dorsolateral prefrontal cortex (DLPFC) (4 studies), followed by hippocampus (3 studies), and others including anterior cingulate cortex (ACC), thalamus and striatum. Among the 4 DLPFC studies, 2, 1, and 1 studies showed an increase, a decrease, and no difference compared to healthy controls in the expression of AMPA, respectively. In the hippocampus, all of 3 studies indicated a decrease. The subjects investigated were heterogeneous in terms of age, sex. Moreover, analysis techniques differed among studies.
Conclusions: The results were not always consistent, which may be due to the heterogeneity of this population and the analysis techniques employed. Moreover, postmortem studies are subject to physiological changes after death. These limitations of the previous studies clearly emphasize the need of examination of AMPA receptors in living human brains as well as comprehensive characterization of subjects.
Supported By: Japan Agency for Medical Research and Development
Keywords: AMPA, MDD, Depression, Glutamate, Postmortem

T109. Reward-Dependent Connectivity With Orbitofrontal Cortex in Subclinical Depression

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Background: A host of neuroimaging studies have shown that unipolar depression is associated with blunted striatal responses to reward. Although a similar striatal deficit emerged in our recent coordinate-based meta-analysis, we also found hyper responses to reward in orbitofrontal cortex (Ng, Alloy, & Smith, in prep), suggesting unipolar depression may be linked to aberrant connectivity between the OFC and ventral striatum.
Methods: To investigate this possibility, we utilized functional data from the Human Connectome Project (HCP), which contains a wide range of data from nearly 1200 participants (Barch et al., 2013, NeuroImage). Our initial analyses focused on 145 participants who engaged in a popular reward-processing task (Delgado et al., 2000, J Neurophysiology).
Results: Consistent with prior studies, we found enhanced activation within VS to receipt of reward (relative to punishment). We next used a psychophysiological interaction (PPI) analysis to investigate how the receipt of reward and punishment influences the connection between OFC and other regions of the reward circuit. Strikingly, we found that receipt of punishment decreased connectivity between OFC and

ventromedial prefrontal cortex (vmPFC), pointing to a potential regulatory link between these two areas. Finally, we examined whether reward-related connectivity was related to subclinical depression. Preliminary analyses indicated a weak correlation between subclinical depression and OFC connectivity ($p < 0.001$, uncorrected).
Conclusions: Overall, our results further current understanding of how depression influences connectivity in the reward system. These results also establish a strong foundation for future analyses aiming to elucidate the relation between corticostriatal connectivity and unipolar depression.
Keywords: Reward, Corticostriatal Connectivity, Neuroimaging

T110. Familial Aggregation of Neurocognitive Deficits Associated With Suicidal Behavior

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Background: The association of neurocognitive deficits with suicidal behavior in depression is well established (Richard-Devantoy, et al., 2014 & 2015). Given that both this behavior (Brent et al., 2015) and traits associated with risk (Melhem et al., 2007) run in families, these neurocognitive deficits may run in families as well.
Methods: Neurocognitive performance was assessed in 192 offspring (mean age 19.4 7.6) of a parent with both a history of major depression and past suicide attempt, and in 215 offspring (mean age 19.0 6.4) of a parent with a history of major depression alone. The majority had not experienced an episode of major depression, and only a small number (19 offspring in each group) made attempts. Three measures previously associated with suicidal behavior were examined, measures of cognitive control (computerized Stroop), memory (Buschke Selective Reminding Test; SRT), and decision-making (Iowa Gambling Task; IGT).
Results: Controlling for family membership in a mixed-model design, offspring of suicide attempter parents performed significantly worse than non-attempter offspring on both the Stroop ($p=.047$) and the IGT ($p=.029$), with performance on SRT non-significant ($p=.110$). With suicide attempters removed, effects remained significant for both the Stroop ($p=.026$) and IGT ($p=.044$).
Conclusions: Mild but detectable neurocognitive weaknesses in cognitive control and decision-making may predate the onset of depression in at-risk individuals and contribute to vulnerability for suicidal behavior. Stroop performance now fulfills three of four criteria of an endophenotypic marker; prospective studies are needed to establish it as such.
Supported By: NIMH
Keywords: Neurocognition, Suicide Risk Factors, Familial Risk, Depression

T111. Changes in Connectivity Induced by White Matter Hyperintensities Predict Dysexecutive Behaviors in Late-Life Depression

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Background: Converging neuroimaging studies indicate that white matter hyperintensities (WMH) disrupt frontal-striatal circuits and contribute to executive dysfunctions in late-life depression (LLD). From FLAIR images, we estimated the effect of LLD's WMH on a set of normal connectomes, projecting the WMH-induced damage onto brain surfaces. We hypothesized that increased WMH-related connectivity loss in frontal-striatal regions would be related to poorer executive function performance and self-reported dysexecutive behaviors in patients with LLD.
Methods: We enrolled 44 patients and 62 age-matched healthy controls (mean age 72.5±6). Dysexecutive behaviors were rated on the Frontal System Behavioral Scale-executive subscale and poorer executive dysfunction performance was assessed with the Trail Making Test (TMT) Trail B subtest and Stroop Interference Test. WMH masks were automatically segmented using FSL's BIANCA and loaded into the Network Modification (NeMo) tool. NeMo estimates the surface-projected Change in Connectivity (ChaCo) by overlapping WMH masks on 73 normal connectomes. Within patients, partial correlations (adjusting for age) were calculated between ChaCo scores, self-reported dysexecutive behaviors and executive performance.
Results: Relative to comparison participants, patients had significantly higher WMH volume ($p=0.01$), worse dysexecutive behaviors ($p<0.001$) and TMT-B ($p<0.01$) performance. Within patients ($n=39$), ChaCo scores in the bilateral caudate, supramarginal and postcentral gyri correlated with dysexecutive behaviors (FDR $q<0.05$).
Conclusions: We showed that NeMo can be used in LLD to successfully identify clinically-meaningful, WMH-induced connectome disruptions from simple, routinely-obtained FLAIR images. As predicted, connectivity loss in the bilateral caudate correlated with dysexecutive behaviors. Correlations with parietal regions suggest dysexecutive behaviors may be sustained by abnormalities extending beyond frontal-striatal circuits.
Supported By: RO1MH097735 (Gunning)
Keywords: Geriatric Depression, Executive Functioning, White Matter Hyperintensities, Structural Connectivity

T112. Impact of Childhood Trauma on Decision Making in Pediatric Bipolar Disorder

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Background: Literature showed that histories of childhood trauma (CT) leads to impairment in affective processing, and is

a risk factor for developing severe forms of BD. Despite a growing literature focused on cognitive impairments in pediatric BD (PBD), few studies explored their interactions with CT. The present study addressed this issue by examining the link between CT and decision making in PBD.
Methods: Sixty PBD (Age: 15.17 ± 1.63 years; 34 girls) were administered the Childhood Trauma Questionnaire, along with the Affective Go/No-go (AGN) and the Cambridge Gambling task (CGT). A hierarchical cluster analysis narrowed down the factors to Sexual Abuse (SA), Physical abuse and neglect (PAN) and Emotional abuse and neglect (EAN). They were entered in mixed linear models for AGN outcomes and factorial ANCOVAs for CGT outcomes, all controlled with age, response time and opposite defiant disorder comorbidity.
Results: In the CGT, the quality of decision making was lower in patients with PAN and EAN histories. Similarly, the quality of decision making and risk taking was lower in patients with SA histories, but only in the absence of PAN histories. In the AGN, the number of omission was higher in patients with EAN and SA histories whose effects compounded in patients with both histories. Once again, PAN histories counteract the effect of SA on the number of omissions.
Conclusions: In PBD, SA and EAN histories are associated with poor decision, making PBD excessively cautious, even less prone to risk taking when both are combined.
Supported By: This work was supported by NIH grant 1R01MH69774 and Pat Rutherford, Jr Chair in Psychiatry at UTHealth.
Keywords: Pediatric Bipolar Disorder, Decision Making, Childhood Trauma

T113. Association Between Inflammatory Markers and Neurocognitive Flexibility Among Adolescents With and Without Bipolar Disorder

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Background: Peripheral inflammatory markers are elevated among adolescents and adults with bipolar disorder (BD), particularly during symptomatic episodes. In adults with BD, inflammatory markers are negatively associated with neurocognitive functioning. This relationship has not been investigated in BD adolescents.
Methods: Participants were 13-20 years old, 63 with BD (31 symptomatic hypomania and/or depression, 32 euthymic) and 60 HC. Diagnoses were confirmed using the K-SADS semi-structured interview. Serum levels of three pro-inflammatory markers (interleukin (IL)-1B, IL-6, and tumor necrosis factor (TNF)) and an anti-inflammatory marker (IL-10) were measured using commercial ELISA kits. Neurocognitive flexibility was assessed via the CANTAB intra/extradimensional shift (IED) task. Multivariate linear regression controlled for IQ and lifetime ADHD.
Results: IL-1B, IL-6, TNF and IL-10 protein concentration levels did not differ by diagnosis. Significant interactions were observed: within symptomatic BD adolescents, but not asymptomatic BD or HC adolescents, lower IL-1B/IL-10 ratio was significantly associated with more errors prior to the extra-dimensional shift ($p=0.023$). Similarly, among symptomatic BD adolescents, but not asymptomatic BD or HC adolescents, lower IL6/IL10 ratio was associated with significantly more trials needed to complete the IED task ($p=0.012$). The models accounted for 13.8% and 13.5% of variance in neurocognitive flexibility, respectively.
Conclusions: Anti-inflammatory predominance was unexpectedly associated with better neurocognitive flexibility among symptomatic BD adolescents, but not among asymptomatic adolescents or HCs. Prospective, repeated measure studies are warranted to verify the direction of these findings.
Supported By: HSF; Brain and Behaviour Research Foundation
Keywords: Inflammation, Bipolar Disorder, Cognitive Flexibility, Child and Adolescent Psychiatry

T114. Depressed Patients With History of Suicide Attempts Differ From Non-Attempters in Processing of Emotional Faces

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Background: Suicide is a leading cause of death worldwide. Better understanding of behavioral and neural characteristics of patients who attempted suicide(SA) may lead to improvements in suicide prevention. We hypothesized that depressed patients with history of attempts will differ from non-attempters(NA) in performance of an emotion classification task and its neural correlates.
Methods: 35 non-medicated MDD patients, of whom 14 had previously attempted suicide, participated in fMRI while performing an emotion evaluation task. Faces were evaluated in two conditions: emotion(positive/negative) or gender(male/female). Reaction time(RT) was collected. Imaging data were processed to generate individual statistical maps, subsequently used in a multivariate whole-brain analysis.
Results: The multivariate analysis of RT revealed an interaction of emotion and condition, ($p=0.04$). Trends were observed for an interaction of emotion and suicide history, ($p=0.08$) and for a three-way interaction of emotion, suicide history and condition, ($p=0.59$). Additionally, SA patients showed a processing bias in faster classifying emotion as positive vs negative (t-test, $p=0.03$) compared to NA. The imaging analysis showed an interaction of emotion with the history of suicide in the left precuneus, and an interaction of condition with the history of suicide in precentral gyrus, right insula and right superior temporal gyrus. Emotion type, condition, and suicide history interaction was found in the left lingual gyrus (FWE-corrected, $p<0.01$).

Conclusions: Our results suggest that depressed SA show a processing bias vs NA while judging emotion, reflected biologically in brain regions crucially involved in the facial and emotional processing. Further analyses will examine relationship of these findings to depressed mood and suicidal ideation.
Supported By: NIMH Intramural Research Program
Keywords: Suicide, Major Depressive Disorder (MDD), BOLD fMRI, Emotional Facial Processing

T115. Perinatal Depression: Majority of Onset Occurs Prior to Delivery, Not Afterward

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Background: The World Health Organization has declared maternal mental health problems like depression, are a major public health challenge associated with substantial morbidity and mortality. Recent research suggests that postpartum depression may manifest in the antenatal period
Methods: We followed 858 women through pregnancy and 3 postpartum months to describe perinatal depression, identify and describe subtypes, course of illness/wellness, and develop predictive models for risk. At 15 timepoints, assessments included established psychometric measures of mood, health history, pregnancy experience and demographics. Multivariate statistical methods included data reduction (factor analysis) and clustering as well as tree-based methods (recursive partitioning and stochastic gradient boosting) to describe and predict incident depression.
Results: Using the Edinburgh Postnatal Depression Scale (EPDS), 9.7% of the sample were categorized as "high probability MDD" at baseline. Of the 176 post-baseline incident cases, 82% occurred prior to delivery. In the 6 prenatal EPDS measurements incidence rates were: 8.7%, 5.8%, 8.4%, 4.8%, 5.7%, and 4.3%. In the postpartum periods, the rates were considerably lower: 2.6%, 2.9%, 2.7%, and 2.8%. Anxiety, stress, and external factors such as being the victim of a crime, and medical conditions such as preeclampsia were predictors of incident cases. Further, we described 3 sets of distinct symptom patterns differing with respect to presence/absence of comorbid anxiety and severity.
Conclusions: This study extends recent findings to suggest that the vast majority of maternal depression occurs prior to delivery, describes distinct symptom patterns across pregnancy and postpartum, and points to the importance of early prenatal screening for mood disorders.
Supported By: Janssen Pharmaceutical Research & Development
Keywords: Postpartum Depression, Maternal Depression, Perinatal Depression, Subtypes, Course of Illness

T116. Atypical Depression and Sleep Patterns Using a Family Study Approach

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Background: Our previous work has shown specificity of the atypical subtype of depression, characterized by increased appetite and sleep. We have shown that there may be common familial factors underlying overweight and atypical depression in families. The aim of this paper was to assess the association between atypical depression and sleep patterns and problems, particularly daytime sleepiness, in order to evaluate if they are also associated with the familial transmission of atypical depression.
Methods: The sample consisted of 387 adult probands and 459 first degree adult relatives who were interviewed in the NIMH Family Study of Affective Spectrum Disorders. Psychiatric assessment was based on structured diagnostic interviews and sleep characteristics were assessed using self-reported Epworth Sleepiness Scale (ESS) and the Diagnostic Interview for Sleep Patterns and Disorders (DISP).
Results: Participants with atypical depression had higher ESS scores compared to controls (p-value$<$0.001). The results of mixed regression models that controlled for age, sex and mood disorders revealed that there was a familial association between ESS scores in probands and relatives (β=0.13, p-value=0.008). Moreover, relatives of probands with atypical depression had increased ESS scores compared to controls (β=1.02, p-value=0.045), after controlling for atypical depression in relatives.
Conclusions: These results showed high comorbidity between atypical depression and sleep patterns and suggest that there may be common familial underlying risk factors that lead to atypical depression and daytime sleepiness. Future studies should evaluate other domains, such as physical inactivity that may explain shared familial risk of atypical depression, sleepiness and weight gain.
Supported By: NIH and the Intramural Research Program (NIMH)
Keywords: Atypical Depression, Daytime Sleepiness, Family Study

T117. Abberrant Approach-Avoidance Tendencies: A Trait-Marker of Bipolar Disorder?

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Background: Mania is characterized by increased pursuit of positive experiences, whereas depression has been related to increased avoidance. However, it is less clear whether these aberrant behaviors can also be observed in euthymic states, which would suggest that they are a trait marker of the disorder. We tested euthymic patients with bipolar disorder with an approach-avoidance task.
Methods: To address this question, we compared the performance of 28 euthymic patients diagnosed with bipolar-I disorder (12 male, mean age = 43.3) during an implicit approach-avoidance task to the performance of 27 healthy volunteers (14 male, mean age = 42.5).

Results: The 2x2x2 ANOVA (picture valence x behavior x group) revealed a significant threefold interaction ($F(1, 53) = 4.16$, $p = .046$). Post-hoc t-test showed that euthymic bipolar patients were slower in approaching pictures with negative valence ($t(53) = -2.01$, $p = .049$) and slower in avoiding pictures with positive valence ($t(53) = -2.41$, $p = .020$).
Conclusions: These findings show that bipolar disorder patients are impaired in resolving approach-avoidance conflicts. Moreover, the fact that our patients had been euthymic for more than two months indicate that this could be a trait marker of the disorder. This is an important finding, because it could help us to develop more precise diagnostic tools, which is important as bipolar disorder is often initially misclassified.
Supported By: DFG
Keywords: Bipolar Disorder, Approach/Avoidance, Trait Marker

T118. Objectively Measured Physical Activity and Sleep and its Associations With Depressive and Anxiety Disorders

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Background: Physical inactivity and poor sleep may play a significant role in the development, progression and treatment of depressive disorders. Although less extensively studied, similar patterns have been found for anxiety disorder. However, many studies relied on self-reported measurements that introduce bias. We aimed to evaluate if objective measures of sleep and physical activity are associated to depressive and/or anxiety disorders.
Methods: 370 participants of the Netherlands Study of Depression and Anxiety participated in a 2-week long combined actigraphy and ecological momentary assessment. A Geneactiv accelerometer measuring at 30Hz was worn on the non-dominant wrist. The GGIR R-package was used to preprocess and calibrate the data. Measures of motor activity (ENMO), time spent in moderate to vigorous physical activity, and sleep were extracted, and compared across healthy controls, remitted depression/anxiety and current depression/anxiety.
Results: Preliminary analyses showed significant differences in ENMO and time spent in moderate to vigorous activity, with persons with a current diagnosis having the lowest activity levels. Also, sleep efficiency significantly differed across groups, with current cases having lower sleep efficiency, but no differences in sleep duration were observed.
Conclusions: This first exploration of the data shows that objectively measured physical activity and sleep are associated with depressive and anxiety disorders, with current cases showing lower activity and poorer sleep. Future planned analyses include functional models in order to study patterns and stability of sleep and activity, using the full richness of the data to get a closer grip on the underlying homeostatic disturbances in sleep and activity.
Supported By: The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum).
Keywords: Anxiety Disorders, Depressive Disorders, Sleep, Physical Activity, Actigraphy

T119. Risk of Insulin Resistance and Obesity Associated With Depression, Inflammation and Satiety Among Young Adults

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Background: Risks of cardiovascular disease (CVD) and adult onset diabetes (AOD) are elevated in patients with depression, inflammation and obesity. This study assessed the risks of correlates of CVD and AOD, insulin resistance (IR) and obesity, associated with depression, inflammation and satiety.
Methods: Subjects were recruited from depressed patient (DP) and non-clinical (NC) populations ages 18-25 without diabetes (enrolled 4/2014-3/2017). The homeostatic model was used to assess IR, BMI assessed obesity, DP subjects were compared to NC subjects (DP/NC), C-reactive protein (CRP) assessed inflammation and leptin assessed satiety. Analyses estimated odds ratios (ORs) of IR and obesity; regression analyses estimated adjusted ORs associated with each of DP/NC, CRP and leptin controlling for potential confounders, including demographics, psychological stress/anxiety, sleep quality, alcohol use, nicotine dependence and blood assays including hemoglobin A1c and homocysteine.
Results: Comparing DP (n=97) to NC (n=106) the odds of IR and obesity were increased 13- and 10-fold. Unadjusted analyses found that CRP, leptin, stress, anxiety and depression were significantly associated with increased IR and obesity. DP/NP was positively associated with CRP and leptin. Regression analyses found increased odds of IR associated with depression (>11X), CRP (>5X) and leptin (>4X). Similar examinations of risks of obesity found increased odds with depression (>8X) and CRP (>6X) but not leptin. Obesity was associated with leptin. Confounders included insomnia and nicotine dependence.
Conclusions: Regression analyses suggested that substantially elevated risks of both IR and obesity are associated with depression and inflammation after controlling for a broad range of potential confounders.
Supported By: Hartford Hospital
Keywords: Cardiovascular Disease, Diabetes Mellitus, Insulin Resistance, Obesity

T120. Prediction Chronicity in Depression: Do Somatic Health Indicators Have Added Value Above and Beyond Psychiatric Characteristics?

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Background: Major depressive disorder (MDD) patients are at risk of an unfavourable course. Various psychiatric characteristics have shown to be predictive of MDD's course trajectory, but whether somatic health further contributes to course prediction remains unclear. This study aimed to identify somatic health indicators (e.g. biomarkers, disease status and lifestyle) that predict 2-year MDD chronicity beyond an extensive list of sociodemographic and psychiatric characteristics.
Methods: Data are from patients with current MDD at baseline (n=903) and 2-year follow-up assessment from the longitudinal Netherlands Study of Depression and Anxiety. Course trajectories were based on psychiatric interview and life-chart data and classified as 1) recovered, 2) recurrent or 3) chronic. We first explored baseline demographic and psychiatric characteristics to identify who is at high risk for a chronic course. Secondly, we examined which somatic health indicators substantially added to the prediction model.
Results: At 2-year follow up, 21% had a chronic episode. Multivariate analyses showed that a chronic episode was independently predicted by older age, younger age at onset, high depressive severity and duration, dysthymia and past-year negative life events (C-statistic=0.76, p<.001). Of the 20 tested somatic health indicators, only two (short or long sleep duration and high interleukin-6), contributed significantly to improving the model (C=0.78, p<.001), although both C-statistics were not significantly different (p=.19).
Conclusions: This study showed that sociodemographic and psychiatric characteristics were reasonable predictors of 2-year chronicity. Sleep duration and inflammation showed a significant, but modest, contribution to the prediction model. Overall, somatic health indicators did not add substantial clinically-relevant predictive value beyond psychiatric indicators.
Keywords: Major Depressive Disorder, Chronic Course, Prediction, Somatic Health Indicators, Biomarkers

T121. Increased Resting State fMRI Entropy Associated With Clinical Response to Ketamine for Treatment Resistant Depression in Adolescents

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Background: The goal of this study was to evaluate the efficacy of ketamine as an intervention for treatment resistant depression in adolescents. In this analysis we examined changes in resting state fMRI entropy associated with clinical response to ketamine.
Methods: 11 adolescents with TRD (7 biological males; 14.5-18.8 years old) completed the study. Each subject participated in 6 sessions of ketamine infusions over the course of 2 weeks. Individual rs-fMRI data (3T Siemens, MB=8, TR=720 ms, 680 volumes) were collected before and after the intervention. Data were pre-processed using FSL tools, and ROI-specific time-courses were extracted using SPM. 134 ROIs, including cortical and subcortical regions from the FSL Harvard-Oxford atlas and cerebellar regions from the AAL atlas, were used for analysis. Global entropy corresponding to rs-fMRI signal complexity was evaluated before and after the intervention for the responder (n=5) and non-responder (n=6) groups.
Results: rs-fMRI entropy changes following the intervention were positively correlated with improvements in the Children's Depression Rating Scale (R2=0.54, p=0.083). The percent change in global entropy was significantly greater for the responder group (M=26.9%, SE=12.7%) compared with that for the non-responder group (M=-12.8%, SE=6.1%), based on a student's unpaired t-test (p=0.025).
Conclusions: Our findings suggest rs-fMRI entropy as a biomarker of mood improvement following ketamine infusions in adolescents with TRD. The observed increase in global entropy amongst ketamine responders may reflect a hyperplastic brain state necessary for recovery in depression.
Supported By: NIH UL1TR000114
Keywords: Adolescent Depression, Ketamine, Resting State fMRI, Entropy and Complexity, Clinical Response

T122. No Hippocampal Volumetric Changes Observed in Patient With MDD Vs. HC Post Ketamine Infusion

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Background: Mood disorders are common mental illnesses that are associated with significant morbidity and mortality, thus the need for novel rapid acting antidepressants is high. Ketamine has been a key candidate in the pursuit of a novel therapeutic. Although the glutamatergic system has been the focus when developing rapid acting antidepressants, the precise mechanism of action of these drugs is not fully understood.
Methods: Structural magnetic resonance imaging (MRI) at 7T was used to determine if changes in hippocampal volume were associated with ketamine infusion in patients with MDD. T1 and T2* weighted images were acquired at baseline, and at 1-2 and 10-12 days post infusion in 32 patients with MDD and 22 healthy controls enrolled in a double-blind placebo-controlled crossover trial of 0.5mg/kg IV Ketamine. Hippocampal subfield volumes were estimated using Freesurfer. Mixed models were used to evaluate 12 subfields plus the total volume to determine group differences at baseline, and the effect of drug on hippocampal volume controlling for baseline volume, and group differences in the effect of drug.
Results: At baseline, the MDD and healthy control groups did not differ on total hippocampal volume or subfield volume. Results suggest possible decrease with ketamine in the left presubiculum for MDD patients but not healthy controls; however, no other significant drug-by-group interactions were observed.

Conclusions: Our preliminary data analysis indicate there are no significant hippocampal volume differences in MDD subjects versus healthy controls following ketamine. Further studies will investigate if baseline hippocampal volumes predict response to ketamine.
Keywords: Ketamine, Neuroimaging, Treatment Resistant Depression

T123. Decreased Fractional Anisotropy as a Marker of Aberrant White Matter Integrity in Unaffected Offspring of Patients With Bipolar Disorder

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Background: Bipolar disorder (BD) is a psychiatric disorder affecting 1-2% of the population. The etiology and pathogenesis of BD are complex and not well understood. There is compelling evidence for genetic contribution to the risk of this familial disease. BD is associated with structural and functional brain abnormalities, some of which have been found in unaffected relatives. These have included white matter (WM) changes identified in voxel-based studies.
Methods: We studied 15 children of patients with BD, 16 pediatric BD patients, and 16 matched controls. Diffusion weighted scans were obtained on a 3T scanned using an echo-planar sequence. Scans were segmented using FreeSurfer, and we studied the difference in fractional anisotropy (FA) in 10 areas selected based on literature.
Results: When we compared FA in between the three groups, we found significant decreases in FA in 5 of the 10 areas analyzed, located in frontal and temporal lobes, and the anterior cingulate. The other 5 areas showed decreased FA, but none reached statistical significance after correction for multiple measurements. We did not find increased FA in any areas of the brain of BD offspring.
Conclusions: Our findings point at decreases in FA as a possible endo-phenotype of BD, as they were found in unaffected children of patients with BD. We identified five areas with significantly decreased FA in this population. Most of these areas were previously found to have morphological and functional changes in adult and pediatric BD, and are thought to play important roles in affected domains of functioning.
Supported By: R01 MH 085667
Keywords: Bipolar Disorder, High Risk, White Matter Microstructure, Diffusion Tensor Imaging (DTI)

T124. Abundance of GABA-producing Gut Bacteria Correlates With Functional Brain Connectivity in Depression

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Background: Increased functional connectivity of the Default Mode Network (DMN), a reproducible biomarker of Major Depressive Disorder (MDD), may be related to low cerebral levels of GABA in MDD. GABA circulates in body fluids and can cross the blood-brain barrier. We hypothesize that lower abundance of GABA-producing gut bacteria is associated with MDD and with elevated DMN functional connectivity.
Methods: 26 depressed patients with HAMD24 $>$ 17 and 15 healthy controls provided stool samples which were analyzed for their genomic contents by American Gut and for their transcriptomic contents by shotgun sequencing. Resting state fMRI was acquired within 3 days of stool sample collection. Scans were parcellated into 277 functional nodes using the system of Power (Neuron,72,665-678). Pairwise functional connectivity was studied between the 38,226 unique pairs of nodes. We performed exploratory analyses of the relationship between the abundance of total Bacteroides species and functional connectivity between each unique nodal pair.
Results: Transcriptome analysis of stool samples revealed that bacterial genes necessary for GABA production were expressed in human intestine and encoded by Bacteroides species. B. massillensis, a high-GABA producing Bacteroides species, was significantly less abundant in stool of participants with MDD (0.26%) than in healthy controls (0.61%) (p=o.038). Exploratory analyses show predominantly inverse correlations between Bacteroides abundance and inter-nodal functional connectivity throughout the brain in the depressed group. These inverse correlations cluster in inter-network connections between the DMN, Salience and Task-Positive Networks.
Conclusions: These results are consistent with our hypothesis that GABA metabolism by members of intestinal microflora may affect functional brain connectivity.
Supported By: New York County Psychiatric Society/APA student research grant to Darya Terekhova
Keywords: Gut Microbiome, Depression, Default Mode Network, GABA

T125. Thalami Shape Differences in Elderly Depressed Patients At-Risk for Suicide

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Background: Suicide in elderlies is three times higher than in younger populations, but no study examined its relationship to cerebral alterations. This study aims to identify cerebral correlates of suicidal behavior.
Methods: High-resolution magnetic resonance imaging was used to measure morphometric changes in 17 depressed suicide attempters (mean age=67.8 ±5.7 years old, 26.7 % male), 33 depressed patient controls with no personal or family history of suicidal behavior (mean age=67.6 ±6.4 years old, 53.3 % male), and 21 healthy controls (mean age=66.5 ±5.1 years old, 20% male). Standard T1-weighted MPRAGE images

were processed using the MAGeTbrain pipeline. General linear modelling predicting volume, surface displacement and surface area to determine differences between groups were performed in R/3.4.0 with RMINC/1.5.0.0 co-varying for age, sex and Hamilton depression (Ham-D) index total score, multiple comparisons were corrected using FDR.
Results: Groups did not differ for age, sex, and education. Patient groups were equivalent on the Ham-D total score. No morphometric differences were found between groups, except in thalami. Suicide attempters exhibited morphometric differences in the medial posterior thalami regions, with highest differences in the pulvinar relative to both control groups. A significant difference was also found between suicide attempters and control groups in the anterior regions of the thalami, with strongest differences in the ventral-anterior nucleus.
Conclusions: Medial-posterior portions of the thalami are known to be related to pain and visual processing, and emotional response whereas anterior regions are involved in memory and motor processing. Alterations in these regions may thus be associated with suicide vulnerability in elderlies.
Supported By: AFSP YIG-0-118-13
Keywords: Suicide, Thalamus, MRI Brain Imaging, Elderly

T126. Brain Responses During Implicit Regulation of Emotional Salience Moderate Antidepressant Treatment Response in Major Depression: Findings From the EMBARC Study

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Background: Selective serotonin reuptake inhibitor (SSRI) antidepressants are a first-line therapeutic for major depressive disorder (MDD), the mechanism of which may be restoration of balance between emotional reactivity and regulatory brain processes. However, there is considerable heterogeneity in neural and clinical phenotypes and responses to SSRIs. Targeted treatment selection necessitates an understanding of how heterogeneity impacts treatment response. Progress has been limited by prior study limitations, i.e. small samples, lack of placebo control, and a suboptimal analytic approach. Here, we present findings from a large, multisite randomized clinical trial in MDD assessing moderators of treatment response to a common SSRI (sertraline) vs. placebo. A well-characterized emotional conflict task was used to assess how baseline brain reactivity to emotional salience and its regulation (normatively characterized by reduced recruitment of salience-sensitive regions) moderate SSRI symptom reduction.
Methods: Patients were randomized to sertraline (n=140) or placebo (n=140) and underwent functional magnetic resonance imaging. Intent-to-treat voxel level linear mixed models assessed how baseline brain activation moderated the effect of sertraline on symptoms.
Results: Only activation during conflict regulation moderated sertraline response (corrected p's < 0.05). Mirroring a healthy phenotype, patients randomized to sertraline (vs. placebo) whom effectively dampened dorsolateral prefrontal, frontopolar, and dorsal cingulate activation showed larger symptom reductions relative to those unable to regulate prefrontal function.
Conclusions: Depressed individuals with an intact prefrontal conflict regulation phenotype are best suited to receive SSRIs. These findings advance efforts towards individualized, neurocircuitry-informed treatment selection in MDD and highlight implicit regulation of emotional salience as a key competency impacting SSRI response.
Supported By: NIMH U01MH092221 and U01MH092250
Keywords: Depression, Sertraline, Imaging, Moderator, Emotion

T127. Blood-Brain Barrier Dysfunction as a Biomarker for Neuroprogression in Bipolar Disorder

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Background: Insulin resistance (IR) and type-2 diabetes (T2D) are associated with a more chronic course of bipolar disorder (BD), poor response to mood-stabilizing treatment, cognitive impairment and adverse changes in brain structure and chemistry. These findings suggest that IR comorbidities, such as microvascular pathology and related blood-brain barrier dysfunction (BBBD), may play a role in BD "neuroprogression". Using our recently developed novel approach for MRI-based assessment of BBB permeability, we aim to present the first mapping and quantification of BBBD in living bipolar patients, and test BBBD as a biomarker for neuroprogression and pharmacoresistance.
Methods: Dynamic contrast-enhanced MRI (DCE-MRI) was used to map BBB permeability in BD patients with- and without-IR (BD+IR, n=22; BD-IR, n=15), healthy controls (HC, n=7) and individuals with IR alone (n=4). Cognitive, psychiatric and clinical information was collected with every scan.
Results: Kernel-density based clustering revealed two distinct groups: patients with high vs low % of brain voxels with BBBD ($p<0.0001$). The high BBBD group (n=11) consists entirely of BD patients, with overall 29.7% (11/37) of all BD patients presenting high levels of BBBD. Notably, patients in the high BBBD group scored significantly worse on the depression scale (p=0.009), with 9 of the 11 patients also having IR. Importantly, the high BBBD group showed microvascular pathology in specific brain regions, primarily left-temporal and medial-frontal cortices.
Conclusions: Our novel BBBD imaging approach identifies a specific brain network with microvascular pathology that may be predictive of neuroprogression and pharmacoresistance.
Supported By: NARSAD, CIHR
Keywords: Bipolar Disorder, Blood Brain Barrier, Neuroprogression, Neuroimaging, Predictive Biomarkers

T128. Medial Temporal Lobe and Subcortical Shape Changes Following Electroconvulsive Therapy in Late-Life Depression

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Background: ECT has been associated with grey matter (GM) volume increase. We aim to localize ECT-induced GM surface area and displacement changes and investigate electrode placement and dose effects on subcortical GM and its relationship to mood.
Methods: 70 patients with late-life depression were treated with right unilateral brief-pulse ECT until remission with 22 non-responders switched to bitemporal ECT. Measures of shape and surface area for thalamus, striatum, pallidum, hippocampus and amygdala were obtained from T1-weighted images using Multiple Automatically Generated Templates Brain Segmentation (MAGeT Brain). All analyses were corrected for multiple comparisons using a 5% false discovery rate threshold.
Results: One week after the last ECT, the hippocampus showed both surface area increases and decreases but no displacements. The greatest surface area changes were detected in bilateral amygdalae, whereas the most pronounced displacement was observed in right basal ganglia and right thalamus. There was a significant effect of electrode placement, with bilateral ECT associated with greater volume increases in left hippocampus, bilateral amygdalae, and left thalamus. There was a significant effect of the number of ECTs on medial temporal lobe GM, with more treatments being associated with greater surface area increases in right hippocampus and bilateral amygdalae. There were no significant associations between structural change and change in mood, nor significant structural changes 6 months post-ECT (n=23).
Conclusions: Structural MRI changes following ECT extend beyond the hippocampus and amygdala to thalamus and basal ganglia, with the degree of increase related to electrode position and number of treatments, not to mood.
Keywords: Electroconvulsive Therapy, Late Life Depression, MR Structural Imaging, Surface-Based Morphometry

T129. Brain Connectivity Changes Associated With a Cognitive-Emotional Training Intervention for Depression

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Background: Recent data suggest that cognitive-emotional training using the Emotional Faces Memory Task (EFMT) reduces symptoms in Major Depressive Disorder (MDD) patients. This study examined whether EFMT training modulated brain connectivity in MDD, and whether modulation related to symptomatic improvement.
Methods: Fourteen MDD patients who completed a 6-week EFMT training regimen underwent 3T fMRI pre- and post-treatment. Image acquisition occurred at rest and during an abbreviated EFMT task. Task-based data were analyzed using Dynamic Causal Modeling to estimate effective connectivity; resting-state data were analyzed to estimate functional connectivity within and between key neural networks. Effect sizes (Cohen's d) for post-treatment changes were calculated; results of $d \geq 0.3$ are reported. Pearson's correlations estimated the relationship between changes in MDD symptoms and fMRI measures.
Results: Post-treatment reductions in within-network connectivity were observed in the dorsal Default Mode Network (dDMN; d=-0.38) and Salience network (SAL; d=-0.36), while connectivity increased between left Central Executive Network (LCEN) and RCEN (d=0.31), between vDMN and dDMN (d=0.31), and between LCEN and both vDMN (d=0.45) and SAL (d=0.53). Post-treatment reduction in effective connectivity from dorsal Anterior Cingulate Cortex to amygdala (AMG) (left: d=-0.44; right: d=-0.32) was observed, as were right-sided increases in connectivity from dorsal Prefrontal Cortex (DPFC) to AMG (d=0.33) which correlated positively with reduction in depressive symptoms (r=0.51, p=0.05).
Conclusions: EFMT may modulate neural circuitry implicated in MDD. Post-treatment reductions in functional connectivity of dDMN and SAL and increased integration between cognitive control, self-referential and salience processing networks suggest increasingly coordinated responses to emotional stimuli in MDD patients.
Supported By: NARSAD Young Investigator Grant (#24100); NIH K23 Award (#5K23MH0992223)
Keywords: Depression, Brain Imaging, fMRI, Cognitive Training, Effective Connectivity, Resting State Functional Connectivity

T130. Clinical Response to ECT for Major Depression Involves Variations in Hippocampal Structural Connectivity

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Background: Electroconvulsive therapy (ECT) is an effective treatment for severe depression. Recent evidence suggests that functional and structural changes occur in right anterior hippocampus with ECT. However, it remains unclear whether variations in hippocampal structural connectivity occur with ECT and relate to clinical response. This study used

functionally defined seed regions in the hippocampus and diffusion MRI probabilistic tractography to determine whether tract volume and diffusion tensor metrics change with treatment and differ between depressed patients and healthy controls.
Methods: 38 patients experiencing a DSM-IV defined major depressive episode were scanned at baseline and again after completing an ECT index series. 33 control subjects matched for age and sex were scanned at similar intervals. Data was processed using FSL, and probabilistic tractography was performed, seeding from the hippocampal region. Tract volume and diffusion tensor metrics were extracted for each subject.
Results: General linear modeling revealed a main effect of response at baseline, with significantly increased tract volume in responders only ($p=0.022$). Linear mixed modeling showed main effects of time (all $p<0.004$), and a time by response interaction (all $p<0.038$), with reductions in mean AD, RD and MD in responders only. All analyses included age and sex as covariates.
Conclusions: Larger tract volume was found in ECT responders, suggesting that greater trait-related hippocampal structural connectivity may predispose patients toward successful treatment outcome. Findings also suggest that mechanisms of therapeutic response may involve changes in myelin and axonal integrity between the hippocampus and other brain regions, where such neuroplastic processes distinguish responders from non-responders.
Supported By: R01MH092301
Keywords: Major Depression, Electroconvulsive Therapy (ECT), Diffusion Tensor Imaging (DTI), Hippocampus, Tractography

T131. KNCQ Channel Opener Ezogabine_x000B_as a Treatment for Depression: A Preliminary Resting State fMRI Analysis

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Background: Preclinical studies utilizing a rodent social defeat stress model of depression have established that hyperactivity of the ventral tegmental area may be involved in the pathophysiology of major depressive disorder. Friedman et al. demonstrated that systemic administration of ezogabine, an FDA-approved KCNQ-type potassium channel opener, normalized VTA hyperactivity as well as depressive behaviors.
Methods: 18 unmedicated subjects with major depressive disorder were enrolled in an open-label trial of ezogabine. Clinical measures of depression and anhedonia were taken over a ten-week period. 16 subjects had a pre-treatment resting state fMRI scan, and of those, 14 had a post-treatment scan. Resting state functional connectivity (RSFC) was computed for two ventral striatal seeds: Bilateral nucleus accumbens and ventral caudate.
Results: Over the duration of the study, there was a significant decrease in depressive symptoms as measured by the MADRS, with an average decrease of 13.7 points, or 44.5% ($F = 21.94$, $p < 0.001$). Reduction in MADRS score from pre- to post-treatment was significantly associated with a reduction in RSFC between the ventral caudate and clusters in the mid-cingulate (peak $z = -4.29$, voxelwise $p < 0.005$, $k = 189$, $a = 0.05$) and posterior cingulate/precuneus (peak $z = -3.82$, $k = 170$).
Conclusions: Ezogabine proved to be efficacious in treating major depressive disorder. The imaging results suggest that it may act by reducing connectivity between the ventral caudate and the cingulate. An upcoming multi-site, double-blind, placebo-controlled study will examine ezogabine's efficacy versus placebo, as well as the specificity of its putative mechanism.
Supported By: NIMH: R61MH111932-01
Keywords: Resting State Functional Connectivity, Depression, Novel Treatments

T132. Cardiac-Related Pulsatility in White Matter in Adolescents With Bipolar Disorder is Elevated and Unresponsive to Acute Aerobic Exercise

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Background: There is increased risk and premature onset of cardiovascular disease (CVD) among adults with bipolar disorder (BD), which is not fully explained by traditional CVD risk factors. Adolescents with BD, who are at risk of accelerated atherosclerosis and early CVD, can inform our understanding of additional factors underlying the brain-heart link in BD. The current study investigates cardiac-related brain pulsatility using resting state functional magnetic resonance imaging (MRI) at baseline and following a neurovascular probe comprised of acute aerobic exercise.
Methods: 54 adolescents, 27 with BD and 27 controls, underwent MRI scanning before and 20 minutes after recumbent cycling. Blood oxygenation level dependent rs-fMRI images were acquired over 5 minutes and volumes were sorted retrospectively based on cardiac cycle timing. We used a Fourier series to model pulsatility in each voxel. The proportion of pulsatile voxels in grey matter, white matter and ventricular CSF was compared between groups.
Results: BD adolescents had a greater proportion of pulsatile voxels in grey ($F=7.41$, $p=0.0091$) and white matter ($F=9.04$, $p= 0.0043$) when compared to controls and after accounting for resting pulse pressure, mania & depression scores. There was a significant session x group interaction for ventricular CSF, whereby pulsatility was more substantially reduced 20 minutes post-exercise in controls as compared to BD adolescents ($F=7.85$,$p=0.0071$) but not grey or white matter ($p>0.18$).
Conclusions: This convenient measure of cardiac-related brain pulsatility distinguishes BD adolescents from controls both at rest and in response to acute aerobic exercise.
Supported By: Brain and Behavior Foundation, Ontario Mental Health Fund
Keywords: Bipolar Disorder, Adolescent, Brain Pulsatility, BOLD Functional MRI, Aerobic Exercise

T133. Prediction of Remission to Pharmacotherapy in Late-Life Depression Using Baseline and Single Dose Neural Activation

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Background: Treatment of major depression often involves a lengthy trial and error process delaying improvement and increases risk of suicide especially in late-life depression (LLD). We have demonstrated changes in neural connectivity following a single dose that depended on future remission. Here we combine connectivity and task-based activation to predict remission.
Methods: Participants with LLD completed a 12-week venlafaxine treatment and underwent functional magnetic resonance imaging (fMRI, at rest and during emotion reactivity and regulation tasks) at baseline and a day following a single dose of venlafaxine. Remitted participants had Montgomery-Asberg depression rating scale (MADRS)<10 for two weeks. We employed principal components analysis, Tikhonov-regularized logistic classification, and least angle regression feature selection to predict remission by the end of the 12-week trial. We utilized ten-fold cross-validation and Receiver-Operator-Curves (ROC) analysis. To determine task-region pairs that significantly contributed to the algorithm's ability to predict remission, we used permutation testing.
Results: The fMRI data yielded a sensitivity of 80% and a specificity of 63%, a 15% increase in accuracy over baseline MADRS, which was further improved by using the change in activation following a single dose. Activation from the frontal cortex, hippocampus, parahippocampus, caudate, thalamus, medial temporal cortex, middle cingulate, and visual cortex predicted treatment remission.
Conclusions: Acute, dynamic trajectories of functional imaging metrics in response to a pharmacological intervention are a valuable tool towards predicting treatment response in late-life depression and elucidating the mechanism of pharmacological therapies in the context of the brain's functional architecture.
Supported By: NIMH R01 MH076079; 5R01 AG033575; K23 MH086686; P30 MH90333; 5R01 MH083660; T32 MH019986
Keywords: Late-Onset Depression, Brain Imaging, fMRI, Prediction of Treatment Outcome, Emotional Reactivity, Emotion Regulation

T134. The Neurocircuitry of Approach-Avoidance Decisions in Depression: Towards a Cross Species Model

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Background: Approach-avoidance (Ap-Av) behaviors are abnormal in major depressive disorder (MDD). Work in non-human primates (NHP) identifies specific neurons that respond to decision parameters (Amemori et al, 2015), in addition microstimulation of the primate anterior cingulate cortex (ACC) and the administration of anxiolytic drugs change decision preferences (Amemori & Graybiel, 2012). To increase translational impact, an Ap-Av task was adapted from NHP studies to be used with human functional magnetic resonance imaging (fMRI).
Methods: Forty-six unmedicated subjects (17 with MDD) completed an Ap-Av fMRI task using reward points and aversive images/sounds. Using computational modelling based on prior NHP work, parametric modulators of aversiveness and reaction time (decision difficulty) were used to identify brain regions tracking these components of Ap-Av decisions.
Results: Across all subjects, whole brain analysis ($p=.05$, FWE) revealed a cluster in the ACC which activated more for conflict (i.e., trials that included the delivery receipt of a punishment when approaching) than non-conflict decisions. This activation was negatively correlated with depression scores ($r=-.511$, $p<.05$). Including aversiveness as a modulator, a cluster was found to track this in the orbital gyrus leading into rostral ACC. Including reaction time as a modulator revealed clusters in the dorsal ACC and insula tracking this.
Conclusions: Modelling from NHP research was used to identify brain regions associated with components of Ap-Av decisions. Data from single cell recordings in NHP targeted comparable regions (ACC), using the comparable parametric modulators and task design. This research lays the foundation for bi-directional models between human and NHP research.
Supported By: R01
Keywords: Approach/Avoidance, Depression, Non-Human Primates, BOLD fMRI

T135. Hippocampal Subfield Volumes and Mixed Depression in Patients With Bipolar II Disorder

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Background: Mixed depression (MxD) is common in bipolar disorder (BD) and associated with worse outcome. The DSM-5 task force coined a mixed feature specifier to include it not only in BDI, but also in BDII. Koukopoulos proposed and validated alternative criteria for MxD to enhance diagnostic sensitivity. There is a lack of studies of its neurobiology. Hippocampal subfields are specifically involved in emotion/mood regulation and in the mechanism of BD. Its role in MxD is unknown. We hypothesized that healthy controls (HCs) and groups of BDII patients subdivided on their lifetime MxD presence/absence would differ in hippocampal volumes.

Methods: Seventy-one patients with BDII, subdivided on whether their lifetime depressive episodes mostly presented mixed features/agitation (N=31) or not (N=40) according to Koukopoulos' and Research Diagnostic Criteria, and 168 HCs underwent high-resolution (3 T) magnetic resonance imaging. Hippocampal subfield volumes were measured through FreeSurfer. Among groups differences were investigated using multiple analyses of variance (ANOVAs) followed by Scheffe tests. Model analysis was preceded by multivariate ANOVA, correcting for multiple comparisons.
Results: Left hemisphere (l) hippocampal subfield volumes differed among groups (Wilks' Lambda=0.81; F=2.93; df =186; P=0.01). We found a significant main effect of MxD on lCA2-3 (F=5.71; df=2; P=0.004) and lCA4-dentate gyrus (DG) (F=4.90; df=2; p=0.008). Patients without MxD presented smaller CA2-3 and CA4-DG than both MxD patients (P=0.01; P=0.02, respectively) and HCs (P=0.008; P=0.02).
Conclusions: MxD are associated in patients with BDII with increased volume on those hippocampal subfields that are specifically involved in neural plasticity, emotional regulation and response to stress.
Keywords: Bipolar Disorder, Depression, Hippocampal Subfields, Neuroimaging, Bipolar II Disorder

T136. Anterior Cingulate Cortex and Depressive Symptoms: A Structural MRI Study

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Background: Several magnetic resonance imaging (MRI) studies have shown significant reduction in anterior cingulate cortex (ACC) volume in people with major depressive disorder (MDD). However, these studies were generally small in size which limited their generalizability. In addition, some MRI studies did not report significant ACC volumetric changes in MDD. This cross-sectional structural MRI study examined the relationship between ACC volume and current depressive symptoms in a large community sample. To our knowledge, this is the largest MRI study of this nature reported in the literature to date
Methods: This study included a total of 1803 adult subjects with brain MRI and Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) scores. Brain volumes were assessed using the Freesurfer program. Multiple linear regression analyses were done to predict right and left ACC volumes using QIDS-SR scores, total brain volume, gender, age, race/ethnicity, tobacco use, alcohol use, and psychotropic medications as predictor variables. Post hoc analyses were conducted by gender and psychotropic medications use.
Results: Right ACC volume (b=-0.61, p=0.007) was inversely associated with QIDS-SR scores, but there was no significant association between left ACC volume and QIDS-SR scores. Furthermore, there was a significant association between QIDS-SR scores and right (b=-0.71, p=0.046) but not left ACC volumes in males, and there was no association between QIDS-SR scores and ACC volume in females.
Conclusions: These results suggest that right ACC volume is reduced in individuals with greater self-reported depressive symptom severity, and this association is stronger in men.
Keywords: Structural MRI, Depression, Anterior Cingulate Cortex (ACC)

T137. Determining Patterns of Activity and Functional Connectivity in Emotion Processing and Regulation Neural Circuitry in Offspring at Risk for Bipolar Disorder

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Background: Recent studies have identified abnormalities in activity and functional connectivity in emotion processing and regulation neural circuitry in youth at risk for bipolar disorder (BD). However, the specificity of these abnormalities to BD and symptoms associated with BD has yet to be elucidated. Our objective was to study these abnormalities and their relationships to symptoms in youth at risk for BD.
Methods: Offspring (ages 8-17) of parents with BD (OBP, n=31), a non-BD psychiatric diagnosis (OCP, n=28), and no diagnosis (OHP, n=21) underwent a functional magnetic resonance imaging scan while performing an emotion processing task and a working memory with emotion regulation task. We used elastic net regression, ANOVA, and correlation analyses to determine group differences in activity, functional connectivity, and symptoms.
Results: Activity and functional connectivity measures explained 51% of the variance in group (lambda=0.553). OBP had significantly increased left caudal anterior cingulate cortex-amygdala functional connectivity compared to OCP when regulating fearful, happy, and neutral emotions (p=0.014, 0.002, 0.001, respectively) and decreased left dorsolateral prefrontal cortical activity compared to OHP when processing angry emotions (p=0.005). OBP had significantly increased manic symptoms compared to OCP and OHP (p=0.032, 0.002, respectively), and manic symptoms negatively correlated with left dorsolateral prefrontal cortical activity to angry faces in OBP (p=0.049).
Conclusions: These findings indicate patterns of increased emotion regulation and decreased emotion processing in prefrontal cortical regions in youth at risk for BD that correlate with increased symptoms of mania. These results contribute to our understanding of underlying mechanisms of, and potential risk factors for, BD.
Supported By: NIMH R01 MH060952-16; NIMH F30 MH111102-01A1
Keywords: Offspring of Parents with Bipolar Disorder, Functional MRI, Functional Connectivity

T138. Serotonin Transporter Occupancy Predicts Default-Mode Network Connectivity: A SPECT and Resting-State fMRI Study

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Background: The serotonergic neurotransmitter system has been implicated in depression and is thought to modulate the default mode network (DMN). However, it is unclear whether serotonergic antidepressants also dose-dependently affect DMN connectivity. Therefore, we investigated the association between serotonin transporter (SERT) occupancy by citalopram and DMN functional connectivity.
Methods: Forty-five healthy female volunteers (mean age=21.6y) participated in a double-dose study. The subjects were randomized to pre-treatment with placebo, low (4 mg; 'low group') or clinically standard (16 mg; 'high group') oral citalopram dose (corresponding to 0%, ~40% and ~80% SERT occupancy, respectively). They underwent a single-photon emission computed tomography (SPECT) scan with [123I]FP-CIT to assess SERT occupancy and subsequently resting-state functional magnetic resonance imaging to assess DMN connectivity. The SERT occupancy in the thalamus was calculated with the cerebellum as reference region. The DMN connectivity was calculated using dual regression in FSL. Non-parametric permutation testing was used to assess the association between SERT binding post-citalopram and DMN connectivity (using Randomise with threshold-free cluster enhancement, $P<0.05$, FWE corrected).
Results: A higher SERT occupancy by citalopram in the thalamus was significantly associated with decreased DMN connectivity with the anterior cingulate cortex (ACC), paracingulate gyrus, postcentral gyrus, superior parietal gyrus and temporal pole.
Conclusions: We demonstrate that higher SERT occupancy by citalopram in the thalamus was significantly associated with decreases in DMN connectivity. This suggests that DMN connectivity might be interesting biomarker, e.g. for treatment monitoring.
Supported By: PrioMedChild
Keywords: Resting State fMRI, Default Mode Network, Selective Serotonin Reuptake Inhibitors, Serotonin, SPECT

T139. Ketamine and Attentional Bias to Threat: MEG Correlates of Stimulus-Evoked Gamma-Band Response

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Background: The glutamatergic modulator ketamine has rapid antidepressant effects in individuals with major depressive disorder (MDD). Thus, modulating glutamatergic transmission may be crucial to effectively treating depression, though the mechanisms by which this occurs are not fully understood. Recent findings suggest that AMPA-mediated glutamatergic neurotransmission following synaptic potentiation leads to increased stimulus-evoked gamma-band responses, which could provide one explanation for how ketamine influences mood.
Methods: Sixteen drug-free patients with MDD participated in a double-blind crossover, placebo-controlled experiment where an intravenous subanesthetic dose of ketamine hydrochloride (0.5 mg/kg) was compared to a placebo-saline infusion scan. Magnetoencephalographic recordings were collected approximately 6.5 hours following both ketamine and placebo infusions. During scanning, the brain correlates underlying facial processing and attentional bias were examined using a dot probe task with emotional face stimuli. We specifically examined the ketamine- and placebo-mediated stimulus-evoked gamma-band responses during attentional bias to threat (i.e., angry congruent versus angry incongruent faces).
Results: A network of regions showed enhanced stimulus-evoked gamma-band responses to angry congruent compared with angry incongruent faces, including bilateral superior parietal lobule, bilateral middle temporal gyrus, bilateral middle frontal gyrus, left superior temporal gyrus, left superior frontal gyrus, and left amygdala. In contrast, no regions showed significantly enhanced gamma-band responses to happy congruent compared with happy incongruent faces.
Conclusions: These findings add to a growing literature showing that attentional bias to threat recruits a network of brain regions. It also adds to a growing literature on stimulus-evoked gamma-band responses following ketamine administration. Ongoing work will model ketamine-mediated fronto-amygdala connectivity.
Supported By: NIMH Intramural Research Program
Keywords: Magnetoencephalography, Major Depressive Disorder (MDD), Ketamine, Gamma

T140. Resting State Amplitude of Low-Frequency Fluctuation is Associated With Suicidal Ideation

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Background: Suicide is a major cause of mortality. Suicidal ideation is a risk factor for suicidal behavior. Patients may have difficulty discussing suicidal thoughts, so a biomarker that assesses ideation would have clinical utility. Previous resting state functional MRI (fMRI) studies of suicidal ideation have used connectivity analyses with specific seeds and targets. Here, we conducted an exploratory whole brain analysis. Neurocognitive function was also considered because it has been associated with both suicidal ideation and resting state activity.
Methods: Thirty-six unmedicated adult subjects with DSM-IV major depressive disorder (MDD) of moderate depression severity and suicidal ideation underwent resting state fMRI scanning; three subjects reported previous suicide attempts. Whole brain analyses of the amplitude of low frequency fluctuations (ALFF) and

fractional ALFF (fALFF) were performed to identify regions in which these measures were associated with Beck Scale for Suicidal Ideation. Group level analysis was performed with FSL/FEAT using a general linear model with a z threshold of 2.3 and a cluster significance threshold of 0.05. A group of 21 healthy volunteers (HV) were assessed for comparison.
Results: Suicidal ideation was positively correlated with fALFF in a region that included the right frontal cortex in MDD. This association remained significant when depression severity was included as a covariate. Secondary analyses found that the fALFF in that region was negatively correlated with percent Stroop interference. Results did not differ between MDD and HV groups.
Conclusions: In a sample of MDD subjects, mostly without a suicide attempt history, suicidal ideation was positively associated with resting state activity.
Supported By: K23
Keywords: Major Depressive Disorder (MDD), Resting State Functional MRI, Suicidal Ideation

T141. Emotion Regulation Abnormalities in Young Adults With Major Depressive Disorder and Adolescent Frequent Marijuana Use

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Background: Major depressive disorder (MDD) is a prevalent, debilitating disorder involving dysfunction in emotion regulation. Long-term effects of frequent marijuana (MJ) use are poorly understood, but early-onset is thought to increase risk for mental illnesses such as MDD.
Methods: We acquired fMRI data to examine brain activation during an emotion regulation task in 19 healthy controls (HC), 18 depressed patients (MDD), 18 frequent marijuana users (MJ), and 16 depressed frequent marijuana users (MDD+MJ). The task involving viewing negative and positive emotional scenes while either attending to, reducing negative, or enhancing positive responses. A factorial design determined the effects of group and task condition, and then participants were sorted into two groups based on a median split of age into early-onset MJ users versus late-onset/non-users.
Results: All results were FWE corrected ($p<0.05$). We detected a main effect of group in right dorsolateral prefrontal cortex (dlPFC), right superior parietal cortex, left temporal lobe, and left insula. MDD and MJ use contributed to functional brain differences uniquely among groups, affecting dlPFC, occipital gyrus, and ventromedial PFC. More pronounced was increased activation in early-onset versus late-onset/non-MJ users in bilateral dlPFC, right medial PFC, right temporal pole, left precuneus, ventral striatum, and insula.
Conclusions: MDD was linked to regions associated with emotion regulation and emotion encoding while MJ use was linked to regions associated with emotion- and reward-processing. Early-onset MJ use was associated with widespread increases in activation regardless of MDD or current MJ use.
Supported By: Ontario Mental Health Foundation
Keywords: Emotion Regulation, Marijuana, Major Depressive Disorder (MDD), Youth, Neural Activation

T142. Intranasal Oxytocin Augments the Efficacy of Psychotherapy for Major Depressive Disorder

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Background: Although both pharmacotherapy and psychological treatments are considered to be efficacious in the short-term treatment of major depressive disorder (MD), at least one third of patients do not respond to treatment and meta-analyses of published and non-published data have found substantially smaller effect sizes than previously reported. In this double-blind pilot randomized control trial (RCT), we assessed whether intranasal oxytocin augments the therapeutic efficacy of psychotherapy for MD.
Methods: Twenty-four volunteers (12 female) with MD underwent 16 sessions of interpersonal therapy, an empirically-supported treatment of MD. Prior to each session, patients self-administered 24 International Units of intranasal oxytocin (Syntocinon) or placebo. Depressive symptoms were assessed with the Inventory of Depressive Symptomatology, Clinician Rating at pre- and post-treatment, and at a six-month follow-up.
Results: A mixed-design Drug X Time ANOVA indicated a robust decrease in depressive symptoms over the course of the study (Time: $F(2, 42)=81$, $p<.001$, $\eta 2=.79$), and that patients receiving intranasal oxytocin showed greater symptom reduction than patients receiving placebo (Drug X Time: $F(2, 42)=3.1$, $p=.056$, $\eta 2=.13$). Effect sizes for the group differences were in the medium to large range and increased from post-treatment (Cohen's $d=0.62$) to follow-up (Cohen's $d=0.84$).
Conclusions: The administration of intranasal oxytocin, relative to placebo, improved psychotherapy outcomes in depressed patients, even at follow-up when oxytocin was no longer being administered. Future RCTs should attempt to replicate these findings using larger samples with different therapeutic modalities, and to determine which patients most benefit from adjunct oxytocin.
Supported By: CIHR
Keywords: Oxytocin, Major Depressive Disorder (MDD), Psychotherapy, Intranasal

T143. Contribution of Mood Symptoms to Early Life Adversity Effects on Executive Function After Risk Reduction Salpingo-Oophorectomy

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Background: Executive dysfunction and depression can occur after risk reduction salpingo-oophorectomy (RRSO) to reduce risk of breast and ovarian cancers. Adverse childhood experiences (ACE) may be one factor contributing to risk vs resilience for cognitive and mood changes after oophorectomy. We hypothesized that ACE would be associated with poorer executive function and that these effects would be mediated by affective symptoms.
Methods: 552 women who underwent RRSO completed the Continuous Performance Task and letter n-back task to probe sustained attention and working memory, respectively. The 10-item ACE questionnaire was used to assess adversity occurring prior to the age of 18. ACE effects on task performance and subjective symptoms of executive dysfunction were examined using generalized estimating equations. Mood (anxiety/depressive) symptoms were evaluated using the Hospital Anxiety and Depression Scale as a mediator of ACE effects on these outcomes.
Results: ACE was associated with greater severity of subjective executive dysfunction (β= 7.1, p=0.0005) and worse performance on both cognitive tasks (CPT β=-0.1, p=0.03; n-back β=-0.17, p=0.007). Mood symptoms, which were in the mild range on average, were a partial mediator of ACE effects on sustained attention (21.3%; 95% CI: 9.3% - 100%) and subjective report of executive dysfunction (62.8%; 95% CI: 42.3% - 100%).
Conclusions: The negative effects of early adversity on executive function are in part mediated by mood symptoms. These data indicate that assessment of current anxiety and depression symptoms should be included in the evaluation of women who report cognitive complaints after RRSO.
Supported By: K24 DA030301 (Epperson), P50 MH099910 (Epperson), R01 AG048839 (Epperson), F30 AG055256 (Shanmugan), Basser Research Center in the Abramson Cancer Center, Susan G. Komen for the Cure Foundation
Keywords: Executive Function, Mood Symptoms, Estrogen, Adverse Childhood Experiences

T144. Elevations in Cortisol Awakening Response in Depressed Adolescents With a History of Non-Suicidal Self Injury

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Background: Major depressive disorder (MDD) is one of the most common mental disorders and is associated with a host of biological anomalies. A subgroup of those struggling with depression engage in non-suicidal self-harm (NSSI), the act of causing harm to one's own body, without the intent of suicide (Muehlenkamp, 2005). There is emerging evidence that adolescents with NSSI have suppressed HPA axis functioning under stress conditions (e.g., Kaess et al., 2012) and elevated cortisol awakening response (CAR) (Reichl et al., 2016). However, research to date has yet to determine if depressed adolescents with or without histories of NSSI differ in HPA axis functioning.
Methods: Participants were 27 adolescents diagnosed with a depressive disorder (mean age = 15.2; 72% female). Diagnosis and history of NSSI was determined using the Kiddie-Schedule for Affective Disorders and Schizophrenia, Parent and Lifetime version. Area under the curve −ground (AUCg) was calculated for repeated cortisol assays during the Trier Social Stress Test and around awakening (CAR).
Results: Results show that contrary to hypotheses, there were no differences between MDD and MDD/NSSI for AUCg during the TSST. Consistent with past research, there was evidence of elevations in AUCg for CAR for MDD/NSSI compared to MDD (F= 5.12, p = .04), accounted for by differences at 30 min after awakening.
Conclusions: These results extend past research suggesting atypical stress system functioning in depressed adolescents with a history of NSSI. Tentatively, elevated AUCg during CAR in adolescents who engage in repeated NSSI may reflect greater expectations of strain in the day ahead.
Supported By: UMN Center for Personalized Prevention Research, UMN Grant-In-Aid, K23MH090216 from the National Institute of Mental Health
Keywords: HPA Function, Non-suicidal Self-Injury, Adolescent Depression, Morning Awakening Cortisol Response

T145. Salivary Alpha-Amylase and Cortisol in Outpatients With Major Depressive Disorder and Other Psychiatric Disorders

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Background: Specific MDD biomarkers could help improve our understanding of MDD pathophysiology and aid in the refinement of current MDD criteria. While salivary cortisol (SC) can differentiate between healthy controls and patients with psychiatric disorders, salivary alpha amylase (sAA), may be a putative candidate biomarker for MDD specifically.
Methods: In a naturalistic cohort of consecutive outpatients, sAA and SC were determined in 833 participants (97 MDD patients, 142 patients with other psychiatric disorders, and 594 healthy controls). Samples were collected at 7 different time points (at awakening, after 30, 45, and 60 minutes, at 10:00 p.m., at 11:00 p.m., and at awakening on day 2).
Results: The mean age of the sample was 43.8 years (SD = 12.9; 63.9% female). Concerning sAA, MDD patients had higher sAA levels upon awakening on two consecutive days (p = 0.049, p = 0.03 respectively), as well as a higher AUCi (p = 0.049) in comparison to both controls and patients with other psychiatric disorders. Concerning SC, levels of evening SC were also elevated in MDD patients (p = 0.05) in comparison to both controls and patients with other psychiatric disorders. SC values after ingestion of dexamethasone on day 2 were elevated in both MDD patients and patients with other psychiatric disorders (p = 0.03, p = 0.047 respectively).
Conclusions: sAA at awakening and not cortisol differentiates MDD from other psychiatric disorders in outpatients. This

suggests that sAA may be a valuable candidate biomarker for MDD.
Keywords: Salivary Alpha Amylase, Salivary Cortisol, Major Depressive Disorder (MDD)

T146. Anxiety-Potentiated Startle Reductions Correlate With Symptom Reduction by Sertraline in Premenstrual Dysphoric Disorder (PMDD)

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Background: Premenstrual dysphoric disorder (PMDD) affects millions of women worldwide, and is thought to reflect suboptimal sensitivity to the GABAergic progesterone metabolite allopregnanolone (ALLO). Anxiety-potentiated startle (APS), evoked by unpredictable threat, is mediated by the ALLO-sensitive bed nucleus of the stria terminalis (BNST), and is used in this study as a marker of GABAergic sensitivity. We hypothesized that luteal (L) phase sertraline treatment will reduce premenstrual mood symptoms, and the magnitude of symptom reduction will correlate with magnitude of APS reduction. We hypothesized that fear-potentiated startle (FPS) to predictable threat, which is not mediated by BNST, will not correspond to symptom reduction.
Methods: Female participants (controls, PMDD) underwent a threat of shock (no/predictable/unpredictable (NPU) shock) acoustic startle task to assesses APS and FPS. In a within-subject design, NPU was administered during the L phase and repeated in the next L phase when PMDD participants were taking 50 mg sertraline QD. PMDD symptom severity was measured with the Daily Rating of Severity of Problems (DRSP) scale.
Results: Among PMDD participants, L phase sertraline reduced premenstrual mood symptoms ($p=0.001$) and APS ($p=0.048$), but not FPS ($p=0.367$). Reduction in PMDD symptoms positively correlated with reduction in APS ($p=0.003$) but not FPS ($p=0.915$).
Conclusions: Improvement in PMDD symptoms correlated with decrease in APS, but not FPS, among PMDD participants, suggesting a role for sertraline in normalizing ALLO-GABA interactions, via its action as a selective brain steroidogenic stimulant (SBSS).
Supported By: NIMH K23, NARSAD Young Investigator Award
Keywords: Acoustic Startle, Premenstrual, GABA, Sertraline, Women's Mental Health

T147. Incidence of Synthetic Oxytocin Administration and Time to Improvement of Depression and Anxiety Symptoms in the UCSD Intensive Outpatient Treatment Program for Postpartum Depression

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Background: Women develop postpartum depression (PPD) at a rate of approximately 15-20%. Oxytocin (OT) — a neuroendocrine hormone that mediates social interactions — is essential in lactation. Pitocin, a synthetic form of OT, is commonly used to induce labor, which has been shown decrease endogenous OT production; this decrease has been implicated in abnormal bonding between mother and infant and in the development of PPD in mothers. Conversely, higher levels of OT in the postpartum period have been associated with lower depressive and anxiety symptoms.
Methods: An intensive outpatient (IOP) treatment program for mothers with PPD was developed at UCSD. Since its inception in March 2017, 25 women have completed the program. Upon admission and discharge, all women undergo the Edinburgh Postnatal Depression Scale (EPDS), Beck Anxiety Inventory (BAI), and Postpartum Bonding Questionnaire (PBQ). A retrospective chart review was utilized to determine incidence of Pitocin administration at time of parturition and analyzed regarding time to improvement of depressive and anxiety symptoms.
Results: Mothers with PPD had symptomatic improvement during the course of IOP treatment. We characterized PPD symptomatology in the new mothers as measured by EPDS, BAI, and PBQ in comparison to Pitocin administration at parturition.
Conclusions: To our knowledge, this IOP is one of only a dozen in the US that offer intensive treatment for PPD. Incidence of synthetic OT administration and severity of depressive and anxiety symptoms is currently unknown. We will present our novel findings, with the eventual goal of determining recommendations to improve outcomes for both mothers and infants.
Supported By: NIH R25 MH101072
Keywords: Postpartum Depression, Oxytocin, Bonding

T148. Daytime Salivary Melatonin Related to Gastrointestinal Symptoms in Young Adults Seeking Psychiatric Care

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Background: The pathophysiology of irritable bowel syndrome (IBS) is not fully understood. Patients with IBS have a high prevalence of psychiatric comorbidity, mainly depression and anxiety disorders. Melatonin is produced in the gastrointestinal tract, and may reduce gut motility. Psychiatric conditions are, in turn, associated to circadian disturbances in peripheral melatonin levels. The aim of this study was to look for associations between salivary melatonin and gastrointestinal symptoms in young adult psychiatric patients.
Methods: Patients, age 18-25 years, seeking psychiatric care with primarily anxiety and/or affective disorders were included in the study. Scores from The Gastrointestinal Symptoms Rating Scale (GSRS) were compared to salivary melatonin measured at six time-points during the waking hours of one day.

Results: Bivariate correlations were found between daytime melatonin levels at several time-points and the symptoms of pain, early satiety, bloating and total GSRS scores. When controlling for possible confounding factors including gender, melatonin levels in saliva 30 minutes after lunch remained significantly correlated to the symptoms of gastrointestinal pain, bloating and total GSRS score.
Conclusions: Elevated salivary melatonin levels after lunch are associated to the IBS symptoms of pain and bloating and are in line with the proposed effect of gastrointestinal melatonin on gut motility. This result furthers our understanding of the mechanisms of IBS linked to psychiatric disorders and circadian disturbances of melatonin secretion.
Supported By: Märta och Nicke Nasvells fund; Anna-Britta Gustafssons stiftelse; Stiftelsen Apotekare Hedbergs Fund; Erik, Karin och Gösta Selanders Stiftelse; Stiftelsen Söderström- Königska sjukhemmet; The Swedish Society of Medicine and Medical Training and Research Agreement (ALF) Funds from Uppsala University Hospital.
Keywords: Melatonin, Irritable Bowel Syndrome, Depression

T149. Do We Have Evidence for Predictive Biomarkers for Major Depressive Disorder? A Meta-Analysis and Systematic Review of Prospective Studies

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Background: During the last century many biological hypotheses have been postulated to underlie the psychopathology of major depressive disorder (MDD). In order to gain insight in the evidence for these hypothesis from patients, a systematical search for longitudinal studies investigating biological factors before the onset of MDD was performed.
Methods: PubMed, PsychINFO, and Embase were used as databases. The search strategy included terms relating to (1) MDD; (2) a longitudinal design or onset/relapse/recurrence; and (3) potential biomarkers. Current leading biological models for depression were covered, including neuroimaging, neurotransmitters, neurotrophic factors, hormones and immunology.
Results: PRISMA guidelines were followed and 46830 articles were initially screened, indication 642 relevant articles that were screened on full text. Eventually, 90 articles fulfilled the inclusion criteria. Results were too heterogeneous or limited to perform meta-analyses for the topics: Neuroimaging (n=19), Gut (n=1), Immunology/inflammation (n=5), Neurotrophic (n=1), Neurotransmitters (n=1), Hormones (n=62), Oxidative stress (n=1). A meta analysis was performed for cortisol, which showed that higher cortisol levels predict a 44% higher chance of developing MDD (n=14, OR: 1.44 [1.12-1.84] $p = 0.004$), but not having a relapse or recurrent episode (n=4, OR: 1.524 [0.801 2.899] p=0.199).
Conclusions: Surprisingly, although a rigorous systematic search for prospective evidence for biomarkers for depression was performed, we found limited prospective studies investigating leading biological models. Only cortisol could be identified as prospective biomarker for depression onset. More prospective studies are necessary to investigate the causes (and consequences) of depression onset, relapse and recurrence.
Supported By: NIAS: Netherlands Institute For Advanced Study in the Humanities and Social Sciences (grant for Claudi Bocktings group)
Keywords: Major Depression, Meta-analysis, Neuroendocrinology, Cortisol, Neuroimaging

T150. Relationship Between Melatonergic and Thyroid Systems in Depression

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Background: Although melatonergic and thyroid system dysregulations are often observed in depression, it remains largely unknown whether these abnormalities are interrelated.
Methods: Plasma melatonin concentrations were evaluated between 9 PM and 8 AM in 12 DSM-5 depressed inpatients; light (2,000 lx) was administered at midnight for one hour with a portable light device. On the following day, TSH responses to 8 AM and 11 PM TRH tests were measured.
Results: Melatonin profiles exhibited a wide interindividual variability. Light induced a reduction in melatonin concentrations ($p < 0.005$); lowest values were observed at 1:13 AM $\pm$ 30 minutes (SD). Melatonin suppression (MT-S) values (expressed as percentage of change between concentration at midnight and lowest concentration after light) were correlated with 11 PM-ΔTSH (rho = 0.60; $p = 0.04$) and $\Delta\Delta$TSH values (difference between 11 PM-ΔTSH and 8 AM-ΔTSH; rho = 0.64; $p = 0.03$). Post-light rise in melatonin (MT-PLR) values (expressed as percentage of change between lowest concentration after light and concentration at 4 AM) were correlated with 11 PM-ΔTSH (rho = 0.78; $p = 0.004$) and $\Delta\Delta$TSH values (rho = 0.59; $p < 0.05$). Moreover, patients with reduced $\Delta\Delta$TSH values (< 2 μU/ml) showed a tendency towards lower MT-S and MT-PLR values (both p=0.07) compared to patients without thyroid abnormality.
Conclusions: Our preliminary results suggest that melatonergic and thyroid systems are interrelated. In depression, a downward trend in nocturnal responses of melatonin (to light) and TSH (to TRH) could possibly result from the weakened output of the endogenous oscillator.
Supported By: APF2R, Rouffach, France
Keywords: Melatonin, TRH Test, Chronobiology, Depression

T151. Serum Levels of GDF-15 are Increased in Bipolar Disorder

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Background: GDF-15 is expressed in activated macrophages in response to inflammation, oxidative stress, telomere erosion, etc. GDF-15 plays fundamental roles in biological processes of aging and is associated with increased risks of a variety of illnesses, including cardiovascular diseases and various malignancies. Recently its role in bipolar disorder has received attention after two proteomic studies showed increased serum levels of GDF-15 comparing patients with bipolar disorder and healthy controls. However, these results have never been directly confirmed in studies that control for psychopathological parameters.
Methods: We consecutively recruited 46 patients with a diagnosis of bipolar I, either in euthymic (N = 23) or manic (N = 23) states as well as 33 age- and gender-matched healthy controls. Inclusion criteria were: 1) aged 18-65 years 2) DSM-IV diagnosis of bipolar disorder, 3) at least of 1 year of illness; 4) no major medical illnesses. Young Mania Rating Scale and Hamilton Rating Scale for Depression were used to assess the severity of mania and depression, respectively. The serum levels of GDF-15 were measured by immunoassay.
Results: The levels of GDF-15 were significantly higher ($p < 0.001$) in patients with bipolar disorder in comparison with healthy controls. In patients, GDF-15 levels correlated with age ($p = 0.003$ e rho = 0.434) and illness length ($p = 0.001$ e rho = 0.502).
Conclusions: This is the first controlled cross-sectional study to specifically investigate GDF-15 in patients with bipolar disorder. Altered levels of GDF-15 corroborate the perspective of bipolar disorder as a condition associated with the aging process.
Keywords: Bipolar Disorder, GDF-15, Aging

T152. Non-Replication of Neurophysiological Predictors of Non-Response to rTMS in Depression and Neurophysiological Data-Sharing Proposal

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Background: Repetitive Transcranial Magnetic Stimulation (rTMS) has been shown to be effective as a treatment for Major Depressive Disorder (MDD). In 2012 we reported three neurophysiological predictors for non-response to rTMS treatment derived from the EEG. These included increased fronto-central increased theta, a low individual alpha peak frequency (iAPF), and a large P300 amplitude at location Pz. Using a newly acquired sample, this study aims to replicate the findings that were reported in 2012.
Methods: Data was gathered in two clinics (Brainclinics Treatment / neuroCare Nijmegen and The Hague, The Netherlands). Data from patients with 1) a primary diagnosis of MDD or Dysthymic Disorder according to the MINI (MINI Plus Dutch version 5.0.0) and 2) a Becks Depression Inventory (BDI) of 14 or higher at intake who were treated with left DLPFC rTMS (10 Hz) or right DLPFC (1 Hz) were included (total N = 106). One-Way ANOVA's were run to test differences between responders (R) and non-responders (NR).
Results: There were no significant differences between R and NR for fronto-central theta ($p > .388$); P300 amplitude at Fz and Pz ($p > .132$); or iAPF ($p = .504$).
Conclusions: Even though the numerical trends and directions of the results were the same for iAPF and P300, we were unable to replicate the earlier reported findings. This study highlights the importance of (an independent) replication of scientific findings. Given the current null-finding, we would like to make our own data available for our academic colleagues to perform future replicative scientific work to reduce the likelihood of future non-replication.
Keywords: rTMS, Major Depressive Disorder (MDD), Non-Response, Electroencephalography (EEG), Data Sharing

T153. Left Versus Right Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression

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Background: Deep brain stimulation to the subcallosal cingulate has emerged as a promising therapy for treatment-resistant depression. To date, all studies have employed bilateral stimulation. Unilateral stimulation may provide efficacy while reducing potential side effects and adverse events.
Methods: Five patients were exposed to unilateral open-label deep brain stimulation to the subcallosal cingulate for 12 weeks each to left and right sides in a double-blind, crossover fashion. After 12 weeks of stimulation to each side, bilateral stimulation was initiated and patients were followed for one year.
Results: No difference was found between left and right unilateral deep brain stimulation to the subcallosal cingulate for 12 weeks. Overall improvement in depression was modest following left, right, and bilateral stimulation. No serious adverse events were associated with surgery or stimulation.
Conclusions: This small study did not demonstrate superiority of left- or right-sided deep brain stimulation to the subcallosal cingulate. After one year of bilateral stimulation, antidepressant efficacy was relatively modest, though one patient did go into remission. These findings contrast with prior open-label trials, but may be more consistent with a recently published, large, sham-controlled study. The current study continues to confirm safety of implantation and use of deep brain stimulation to the subcallosal cingulate for patients with treatment-resistant depression.
Supported By: Dartmouth College and Dartmouth-Hitchcock Medical Center
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Subcallosal Cingulate

T154. Electroconvulsive Therapy Induces Age-Dependent Volume Increase in the Human Dentate Gyrus

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Background: Previous preclinical studies in both rodents and non-human primates have reported that electroconvulsive stimulation (ECS), an animal model of ECT, modulates neuroplasticity in the dentate gyrus in the hippocampus. Although several magnetic resonance imaging (MRI) studies have consistently observed ECT-induced hippocampal volume increases, there is little evidence regarding the impact of ECT on the human dentate gyrus.
Methods: Structural MRI was performed in patients with major depressive episode with melancholic features before and after one course of bilateral ECT. Volumes in the dentate gyrus were estimated using a multiatlas segmentation tool (MAGeT-Brain). Paired-t tests were used to examine longitudinal volume changes before and after ECT. A multiple regression analysis was used to investigate the effect of clinical demographics (i.e. age) on volume changes.
Results: Twenty-one depressed patients (mean age (SD), 67.4 (8.4); 15 female; 5 patients with bipolar disorder; 16 patients with psychotic features) participated in this study. Volume in the right CA4/dentate gyrus increased after ECT ($t = 3.61$, $p = 0.002$). A multiple regression analysis revealed that volume increases in the dentate gyrus were associated with age ($\beta = -0.50$, $p = 0.005$) and clinical remission ($\beta = 0.47$, $p = 0.008$).
Conclusions: The current study revealed ECT-induced age-dependent volume increases in the human dentate gyrus. Our results are in line with the results of previous preclinical ECS studies, and support the neurotrophic hypothesis of depression and antidepressant effects.
Keywords: Electroconvulsive Therapy (ECT), Magnetic Resonance Imaging, Hippocampal Subfields, Mood Disorders, Hippocampal Neuroplasticity

T155. Augmenting CBT With Real-Time fMRI Amygdala Neurofeedback Training Increases Early Response to Therapy

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Background: Patients undergoing cognitive behavioral therapy(CBT) for major depressive disorder(MDD) are less likely to relapse when they experience a "sudden gain:" a 25% between-sessions drop in BDI scores during the first third of therapy. The current study examined whether augmenting CBT with real-time fMRI neurofeedback (rtfMRI-nf) to increase the amygdala response to positive memories, which uses principles of CBT including restructuring emotional processing towards the positive and enhancing feelings of sense of self-efficacy, increases the number of participants who experience a sudden gain.
Methods: Sixteen MDD participants completed two rtfMRI-nf sessions before receiving ten weeks of CBT. Nine participants received amygdala rtfMRI-nf and seven received rtfMRI-nf from a parietal control region. Depressive symptoms were assessed via BDI-II during the first three weeks and final two weeks of CBT.
Results: Of participants who completed the prescribed course of CBT, 6 (67%) from the experimental and 3 (43%) from the control rtfMRI-nf group met criteria for sudden gain. The difference between groups in the percent drop from baseline to week 3 of therapy approached significance (BDI decrease of 40% in the amygdala group versus 22% in the control group, $p=0.08$, $d=0.86$).
Conclusions: Patients who received rtfMRI-nf training to increase amygdala response to positive memories showed greater symptom improvement and a higher proportion experienced sudden gains during first three weeks of CBT relative to controls. As experiencing sudden gains during CBT is associated with better long-term outcomes, our results suggest that enhancing positive emotional processing through rtfMRI-nf training prior to cognitive-behavioral treatments for depression facilities the treatment.
Supported By: NIMH 4R00MH101235-03
Keywords: Real-Time fMRI Neurofeedback, Major Depressive Disorder (MDD), Cognitive Behavior Therapy, Amygdala, Positive Memory Recall

T156. Use of Electrical Field Modeling to Predict ECT Response

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Background: Electroconvulsive therapy (ECT) is the most effective intervention for treatment-resistant depression, yet its mechanism of action is unknown. Identifying neural targets by which ECT exerts its effect could inform other neuromodulatory techniques and could lead to precision medicine. In this study we used electrical field modeling, a novel approach, to explore the spatial distribution of electrical current and its interaction with the human brain.
Methods: The GEMRIC (Global ECT-MRI Research Collaboration) consortium collected baseline structural MRI scans in 282 patients with major depressive disorder who subsequently underwent electroconvulsive treatment. Patients were followed clinically and measured HAM-D or MADRS on consecutive visits. Based on the structural scan and the electrode placement we calculated a high-resolution 3-D map (simNIBS) of the electrical field of the ECT for each individual. These individual maps were then used to predict clinical response.
Results: The preliminary results of the first 21 individuals with bilateral electrode placement who were processed showed a significant correlation in the subgenual cingulate cortex,

indicating that higher engagement of this area led to a faster and more robust response. Subsequent analysis of the rest of the database is currently underway.
Conclusions: Taking advantage of the largest ECT MRI cohort we have sufficient power to evaluate the effect of electrical field distribution on clinical response and could shed light on the mechanism of action of ECT. Target engagement differences due to the idiosyncrasy in the anatomical structure of the human brain can lead to a significantly variable response to otherwise identical neuromodulatory approaches.
Keywords: Electroconvulsive Therapy (ECT), MRI Brain Imaging, Electrical Field Modeling, Depression

T157. Using Real-Time fMRI Neurofeedback as a Tool for Demonstrating Therapeutic Efficacy

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Background: Cognitive behavioral therapy (CBT) focuses on changing inaccurate, negative thoughts and behaviors. Two challenges of CBT are sustaining gradual, incremental behavioral changes and measuring biological changes. We aimed to show individuals an index of biological change based on therapeutic experiences via real-time functional magnetic resonance imaging (rtfMRI) neurofeedback. Specifically, our goal was to provide participants with a link between strategies used to cope with negative moods and resultant brain-based biological change.
Methods: Participants (N=13) provided a list of negative memories/worries and cognitive strategies. During baseline COUNT trials, participants counted backwards. During MEMORY trials, they viewed phrases describing their negative memories/worries. During STRATEGY trials participants viewed a strategy used to process the memory/worry. During neurofeedback runs, participants viewed a feedback summary after each MEMORY and STRATEGY trial as an index of how brain activity from their cingulate cortex changed in response to negative memories/worries and therapeutic strategies.
Results: The neurofeedback "strength" (cingulate activation for STRATEGY − MEMORY trials) correlated with self-reported immediate post-scan strategy efficacy ratings and predicted strategy efficacy and frequency ratings one month post-scan (all $p<0.05$). Activation within the periaqueductal gray nucleus, insula, and temporal pole predicted self-reported frequency of strategy use one month post-scan session (whole brain, cluster corrected with FSL Flame 1 to $p<0.05$).
Conclusions: Providing individuals with a demonstration of how using cognitive strategies to regulate negative memories/worries predicted strategy efficacy and frequency of use one month later. Activation in regions associated with physical and emotional pain (e.g., PAG) were engaged when using strategies to regulate sad memories/worries.
Supported By: R01MH9703

Keywords: Real-Time fMRI Neurofeedback, Major Depression, Cognitive Behavior Therapy

T158. High-Dose Theta-Burst Transcranial Magnetic Stimulation Modulates Heart Rate Variability

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Background: Depression is linked to brain changes as well as dysregulation in the autonomic, cardiovascular, endocrine and immune systems. It is accepted as a systemic illness, likely in part related to impaired stress responses. Prefrontal cortex activity is decreased in depressed patients, and a convergence of basic and clinical evidence also indicates that output from the prefrontal cortex modulates autonomic nervous system function; this has been previously shown using heart rate variability, a measure of cardiac autonomic tone. One neuromodulation technique, transcranial magnetic stimulation, may be able to improve the function of this tract and thus stress response.
Methods: In this study we modulate a biomarker for autonomic nervous system function, heart rate variability (HRV), using a novel form of transcranial magnetic stimulation (TMS). We exposed 7 right-handed subjects with major depressive disorder (MDD) to stressful and benign visual stimuli and measured HRV before and after high-dose theta-burst stimulation (TBS) TMS. TBS was applied to the dorsolateral prefrontal cortex (DLPFC) as determined by fMRI targeting and neuronavigation software.
Results: We observed an increase in the high frequency component of HRV following TBS. The high frequency component of HRV is considered indicative of parasympathetic tone. This change was significant only during periods of stressful, and not benign, visual stimuli ($p<0.05$).
Conclusions: These results suggest that TBS TMS may be capable of improving physiological stress responses, though further study in a larger sample is required. It also demonstrates the possible value of tracking HRV as an indicator of TMS target engagement and effectiveness.
Supported By: This work was supported by the Miller Foundation, Stanford Psychiatry Chairman's Small Grant, Stanford CNI Innovation Award, NIH T32 035165, NIH UL1 TR001085, Stanford Medical Scholars Research Scholarship, NARSAD Young Investigator Award and the Gordie Brookstone Fund.
Keywords: TMS, Heart Rate Variability, Major Depressive Disorder (MDD), DLPFC

T159. Effect of Ketamine on Prefrontal Cortex Excitability in Treatment Resistant Depression

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Background: A single intravenous administration of ketamine (0.5 mg/kg) in patients with Treatment Resistant Depression (TRD) induces dramatic improvement in depression symptoms within 4 hours and 65-70 % of patients are deemed responders at 24 hours. Ketamine causes early increases in glutamate-excitatory drive that initiate downstream synaptic plasticity cellular processes in prefrontal cortex (PFC)-limbic regions in animal studies. The neural mechanisms that underlie the ketamine antidepressant effects in TRD is still unclear. Cortical excitability could be a non-invasive biomarker to directly test ketamine related enhanced excitatory neurotransmission.
Methods: Ketamine 0.5 mg/kg for 40 minutes was administered as intravenous infusion to TRD patients (n=4) and left PFC excitability was examined using concurrent transcranial magnetic stimulation-electroencephalography (TMS-EEG) before, 4 and 24 hours after ketamine infusion. Local field power (LFP) is a rectified measurement of the time-locked activity evoked by the TMS pulse and demonstrates the discrete periods of synchronous neural activity (maxima) recorded relative to a given region of the cortex. Maximum LFP value of the early deflection of the TMS evoked pulse was examined as a measure of cortical excitability.
Results: Three out of 4 patients responded to ketamine based on reduction in depression symptoms. Ketamine responders showed lower LFP of the P25 component of TMS pulse at baseline and LFP increases at 4 and 24 hours post ketamine infusion. Non-responder patient showed relative decrease in LFP.
Conclusions: The preliminary result show initial feasibility of TMS-EEG approach to examine the effect of ketamine on PFC excitability and study its relationship with antidepressant response in TRD.
Supported By: Departmental supplement, UTHealth
Keywords: TMS-EEG, Ketamine, Treatment Resistant Depression, Prefrontal Cortex, Cortical Excitability

T160. Novel Biomarker for Bipolar Disorder: Sonic Hedgehog Protein

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Background: Research into identifying the molecular causes of bipolar affective disorder (BPAD) has been disappointing. The molecular genetics of this study builds on decades of Amish longitudinal research revealing co-segregation of BPAD and Ellis-van Creveld (EvC) dwarfism where no EvC individual has been diagnosed BPAD. The DNA change causing EvC confers protection from BPAD by disrupting ciliary sonic hedgehog (Shh) signaling. Molecules in the sonic hedgehog signaling pathway converge with Wnt/β-catenin signaling which play critical roles in mood stabilizing and antidepressant treatments: lithium, valproate, SSRIs, and ECT. The fact that the Amish EvC DNA change disrupts Shh signaling and blocks BPAD strongly suggests that a molecular change causing BPAD does so by altering Shh pathway expression. In this study, we will compare the serum levels of Shh protein in bipolar I individuals to the Shh serum levels in controls
Methods: Cross sectional assessments of Shh serum levels (by enzyme-linked immunosorbent assay, ELISA) in SCID diagnosed bipolar I depressed (MADRS >7) individuals versus matched controls without mental illness history were assessed.
Results: No statistically significant difference of Shh levels between initial 7 cases and 6 healthy controls (3088.2±3700.4 vs. 1644.6±1137.0, p=0.38). Removal of two outliers (HC203 and BP105) still did not reach a significant difference 1711.6±591.3 vs. 1187±217.5, p=0.15.
Conclusions: This small sample pilot evaluation revealed no difference between bipolar I depressed individuals and euthymic controls in serum Shh level. Alternatively, peripheral serum levels may not reflect actions of neuronal signaling. Removing outliers, a sample size for p<0.01, power of 90% would need 68 subjects.
Supported By: Faculty Scholar Award, University of Massachusetts Medical School
Keywords: Bipolar Disorder-I, Molecular Biomarkers, Molecular Genetics

T161. Long-Term Potentiation-Like Visual Evoked Potential Plasticity in a Large Sample of Healthy Volunteers: Effect Sizes and Response Rates

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Background: Synaptic dysfunction is one of the leading candidate mechanisms across psychiatric illnesses, yet progress has been hampered by a lack of methods for non-invasive measurements of synaptic function and plasticity in humans. Plasticity of the visual evoked potential (VEP) is a promising assay for in vivo assessment of cortical long-term potentiation (LTP)-like plasticity. Here, we examined response rates and effect sizes of VEP plasticity in 144 healthy volunteers (HVs).
Methods: One hundred and forty-four HVs (71 females; mean age 37.4±10.0, age range 19-74) underwent electroencephalography. VEPs were evoked by checkerboard reversals (check size=0.5°; random interstimulus intervals of 500-1500msec) at baseline and 2 (POST1), ~26 (POST2), and ~49 (POST3) mins after a modulation block. In the modulation block, VEPs were evoked by 10 mins checkerboard reversals (check size=0.5°; fixed interstimulus interval of 500 msec). VEP plasticity was computed by subtracting individual baseline VEP peak amplitudes from corresponding POST1-3 amplitudes, and response rate was defined as the proportion of HVs showing the expected amplitude changes.
Results: Highly significant VEP plasticity of the C1, P1, N1, and the P1-N1 peak-to-peak amplitudes was found, with most robust effects at POST1 (C1: d=0.71, P=2.5e-14; P1: d=0.76,

P=8.8e-16; N1: d=0.21, P=0.01, and P1-N1: d=0.67, P=3.5e-13). Highest response rates at POST1 were found for plasticity of C1 (83%), P1 (79%), and P1-N1 (78%).
Conclusions: The results suggest that VEP plasticity is a robust and accessible method for non-invasive studies of LTP-like cortical processes which may help elucidate the pathophysiological and clinical significance of synaptic dysfunction in psychiatric disorders.
Supported By: This study was funded by the Research Council of Norway, the South-Eastern Norway Regional Health Authority, Oslo University Hospital, the Ebbe Frøland foundation, and a research grant from Mrs. Throne-Holst.
Keywords: Long-Term Potentiation (LTP), Visual Evoked Potential, Synaptic Plasticity, Synapse

T162. High-Dose Spaced Theta-Burst Transcranial Magnetic Stimulation as a Rapid-Acting Anti- Depressant in Highly Refractory Depression

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Background: The FDA-approved rTMS approach requires 6 weeks to apply 90,000 magnetic pulses, and ~30% of patients achieve remission. We sought to examine a patterned theta-burst stimulation (pTBS) methodology as a method for producing rapid antidepressant action through patterned excitation of the established treatment-resistant depression (TRD) target, left dorsolateral prefrontal cortex (L DLPFC).
Methods: Adults (N=6) who were 21-70 years old with TRD [≥20 on the Hamilton Rating Scale for Depression (HRSD17) and rating of 14/15 on the Maudsley Staging Method with failure to respond to 1) ≥7 antidepressant medications, 2) course of psychotherapy, 3) ≥1 course of traditional rTMS, and 4) failure/intolerance to electroconvulsive therapy (ECT)] were recruited. Participants were stimulated with pTBS over the L DLPFC for 5 days for a total of 90,000 pulses delivered at depth-adjusted 90% resting motor threshold (rMT).
Results: The 6 participants with an average entry HRSD17 of 28.8 (SD 6.05). The mean improvements from pre-stimulation baseline on the HRSD17 were 21.83 (76% change from baseline) for these 6 TRD patients. Reductions in HRSD17 scores were statistically significant immediately post stimulation course (p= 0.0033) as well as on the MADRS (p=0.0014) and the BDI II (p=0.0131).
Conclusions: Patterned theta-burst stimulation (pTBS) over L DLFPFC is a new neuromodulation approach that in open-label usage resulted in remission of major depression in four of six individuals and response in one individual all with severe TRD.
Supported By: This work was supported by the Miller Foundation, Stanford Psychiatry Chairman's Small Grant, Stanford CNI Innovation Award, NIH T32 035165, NIH UL1 TR001085, Stanford Medical Scholars Research Scholarship, NARSAD Young Investigator Award and the Gordie Brookstone Fund.
Keywords: Repetitive Transcranial Magnetic Stimulation, Theta Burst, Depression, Brain Stimulation

T163. Chronic Vagus Nerve Stimulation Significantly and Uniquely Improves Quality of Life in Treatment-Resistant Major Depression

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Background: Vagus nerve stimulation (VNS) is FDA-approved for treatment-resistant major depression (TRMD). Several studies have demonstrated additional VNS benefits on anxiety, cognition, and other depression comorbidities. In this analysis, we hypothesized that adjunctive VNS (VNS+TAU), vis-à-vis treatment as usual (TAU, any antidepressant treatment), would demonstrate greater quality of life (QOL) improvement in a large population of TRMD patients.
Methods: Changes in QOL and depression severity were collected in 795 TRMD patients receiving treatment over five years (301 TAU;494 VNS+TAU) using the Quality of Life Scale Short Form (QLESQ-SF) and the Montgomery Asberg Depression Rating Scale (MADRS), respectively.
Results: Over five years, a statistically significant improvement in QOL was observed in the VNS+TAU group over the TAU group. A regression analysis demonstrated superior improvement in QOL in the VNS+TAU cohort regardless of the reduction in depression, i.e., at every percent drop in MADRS the VNS+TAU group experienced a greater QOL change ($p < .0001$). Compared to similar depression treatment QOL studies, TRMD patients receiving VNS+TAU reported significant QOL improvement with a MADRS score drop of only 34%, considerably below the standard 50% drop associated with antidepressant "response".
Conclusions: This study demonstrates: 1) adjunctive VNS brings about greater QOL improvement in TRMD than TAU; 2) for the same degree of improvement in depression, VNS+TAU improves QOL more than TAU. These findings suggest that VNS is improving QOL beyond simply reducing depressive symptoms; VNS long-term outcomes are likely better estimated with QOL measures than standard depression rating scales.
Supported By: LivaNova
Keywords: Treatment Resistant Depression, VNS, Quality of Life

T164. A Computational Model of Antidepressant Drug Effects

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Background: Less than half of depressed patients taking antidepressants experience complete depression relief. The

reason for this clinically observed heterogeneity in antidepressant response is not yet understood.
Methods: We developed a computational model that represents the interactions between the monoaminergic neurotransmitter-producing brain regions and the hypothalamic-pituitary-adrenal (HPA) axis. Machine learning was used to optimize model parameters to bring it in line with experimental observation. The trained model was used to predict the efficacy of acute drug combinations and characterize the many ways that the model can neuroadapt to simulated chronic drug administration by adjusting receptor strengths.
Results: Our machine learning approach trained the model to reproduce the effects of 48 different acute inputs (drugs, lesions, or hormones) on model outputs (neural unit activation, transmitter levels, or hormone levels). The trained model demonstrates both antagonisms and synergisms between the drugs, and shows that as the number of drugs in the combination increases beyond 15 drugs, the antagonisms counteract the synergisms. When the model was used to simulate administration of chronic drugs and combinations, the model found that the brain could reach similar levels of neuroadaptation in many ways, but not all adapted configurations were also associated with therapeutic monoamine levels.
Conclusions: Simulated acute drug combination experiments suggest that acute drugs may be more effective in combination than individually. The combinations that elevated monoamines closest to therapeutic levels were Venlafaxine/MAOI and Venlafaxine/MAOI/Oxytocin. Furthermore, our neuroadaptation model provides an explanation for the clinical reports of heterogeneous clinical outcomes among patients chronically administered the same antidepressant drug regimen.
Keywords: SSRI, Monoamines, Serotonin, Depression, Neural Networks

T165. Development of an fMRI-Compatible Acute Stress Paradigm: Optimization and Initial Results

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Background: Disrupted stress circuitry has been implicated as a key contributor to major depressive disorder (MDD). This project aimed to elicit a cortisol response to confirm the effectiveness of a modified acute stressor for use in an MRI scanner.
Methods: An initial 11 healthy volunteers received hot and cold stimulation delivered through an MR compatible thermode, while answering arithmetic problems under social evaluation (pilot 1). To increase stress potency, 12 additional participants underwent a traditional stressor, using ice-cold water instead of hot and cold stimulation (pilot 2). Salivary cortisol was obtained pre-stress, and 20 and 40 minutes post-stress. To confirm stressor potency in a clinical population, subjects with current MDD (n=11), remitted MDD (n=15), and healthy controls (n=16) completed the traditional stressor. Salivary cortisol was collected immediately before, 38, 60, and 81 minutes after stress.
Results: There was no effect of stress on cortisol in pilot 1 ($p=.252$). However, in pilot 2, a paired t-test revealed a significant increase in cortisol (ug/dL) from baseline to 20 minutes post-stress induction ($p=.040$). In the clinical investigation, participants exhibited significant increases in cortisol 38 minutes post-stress ($p<0.001$). The MDD group showed a trend-level sustained increase in cortisol at 81 minutes ($p=0.093$), while remitted MDD and healthy controls returned to baseline.
Conclusions: These findings indicate that traditional stress induction using ice-cold water elicits a cortisol response more effectively than an MR safe thermode. This optimized stressor produced an altered stress response in current but not remitted MDD, suggesting a potential state biomarker of depression.
Supported By: RO1
Keywords: Depression, Stress, Cortisol, fMRI

T166. Diabetes and Bupropion in the Treatment of MDD

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Background: The role of inflammation in the pathogenesis of multiple diseases is a relatively recent development in psychiatry and in medicine in general. Inflammation has been implicated in the development of type 2 diabetes and has also been linked to depression in these patients through the Dopamine pathways. Following is a study of the effect of Bupropion compared to SSRIs on the outcome of depression in diabetic patients.
Methods: A retrospective chart review was performed on all diabetic patients with major depression in an outpatient psychiatric clinic. Data collected included demographics, medication history, medical history, current diagnoses, and PHQ-9 scores from every visit.
Results: 105 patients were followed over 5 years. In diabetic patients diagnosed with MDD, there was a statistically significant improvement in patients given Bupropion versus SSRI's. At the last recorded visit patients on Bupropion had lower average scores than those not on Bupropion (8.1 vs. 10.1 at intake, $p<.01$). Patients on other medications improved less, with those on SSRIs having an average score of 8.9 vs 9.9 at intake, and those on SNRIs averaging 9.2 vs 9.9. Neither difference was significant.
Conclusions: The Dopamine enhancing Bupropion was associated with a larger decrease in PHQ9 scores than other antidepressants. This study was limited by its small size, absence of data on inflammation markers status, and on the adequacy of diabetes control in these patients though the results are promising. More research needs to be done to see if Bupropion is more effective at treating depressed patients with other inflammatory illnesses as well.
Keywords: Bupropion, Diabetes, Inflammation, MDD

T167. Measures of Activity- and Energy-Related Gait Variables as Behavioral Biomarkers of Bipolar Disorder: A 6-Month Longitudinal Study

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Background: Quantitative information about the association between mood symptoms and motor behavior in bipolar patients (BP) is very limited. We investigated activity- and energy-related gait variables in BP and healthy controls (HC) at baseline and 6-month follow-up sessions.
Methods: We analyzed baseline data from 31 BP (5 hypomanic; 14 euthymic; 12 depressed) and 14 HC, and longitudinal data from 24 BP and 13 HC. We assessed mood symptoms using Patient Health Questionnaire (PHQ-9) and Altman Self-Rating Mania Scale (ASRM), and gait using an optoelectronic motion capture system and force platforms.
Results: Gait speed (m/s), and peak braking and vertical forces (fraction of body weight) were greater for hypomanic BP (mean±SD=1.48±0.21; 0.25±0.07; 1.22±0.18, respectively) compared to euthymic BP (1.21±0.15; 0.18±0.03; 1.09±0.09, respectively), depressed BP (1.14±0.26; 0.16±0.05; 1.06±0.09, respectively) and HC (1.22±0.12; 0.18±0.03; 1.07±0.06, respectively) (one-way ANOVA with Tukey correction; all $p<0.05$). Changes in gait speed, and peak braking and vertical forces between sessions were similar between BP (-0.02±0.17; 0.00±0.04; -0.01±0.12, respectively) and HC (-0.03±0.16; 0.01±0.03; 0.03±0.09, respectively) (independent t-tests; all $p>0.05$). Within BP, changes in peak vertical force between sessions showed significant negative correlation with changes in PHQ-9 scores (R-squared=0.180; $p<0.05$) but not with changes in ASRM scores (R-squared=0.047; $p>0.05$). Correlations between changes in other variables and mood scores were not significant (all $p>0.05$).
Conclusions: Activity- and energy-related gait variables were mood-specific, and stable between sessions for BP. Changes in energy-related gait variables were associated with changes in mood symptoms, supporting further investigation of gait variables as behavioral biomarkers to predict mood symptoms for BP.
Supported By: This work was supported by Heinz C. Prechter Bipolar Research Fund; American Society of Biomechanics (Kang); Blue Cross Blue Shield of Michigan Foundation (Kang); and University of Michigan Rackham Graduate School (Kang).
Keywords: Bipolar Disorder, Behavioral Biomarkers, Gait, Activity, Energy

T168. Microvascular Responsiveness to Serotonin is Altered in Young Adults With Major Depressive Disorder

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Background: Dysfunction of the brain serotonergic system is implicated in the pathogenesis of Major Depressive Disorder (MDD). Serotonin (5-HT) is additionally a vasoactive molecule, mediating its effects, in part, via nitric oxide (NO)-dependent mechanisms. Selective serotonin reuptake inhibitors (SSRIs) also modulate vascular regulation. Despite its role in the neurobiology of depression, the effect of 5-HT in the vasculature of adults with MDD remains unexplored. We hypothesized that 5-HT-mediated vascular responsiveness would be altered in adults with MDD via NO- and 5-HT reuptake-dependent mechanisms.
Methods: Six healthy adults (HC; 3 men; 23±2yrs) and 6 otherwise healthy adults with MDD (non-medicated; 2 men; 23±2yrs), classified via the diagnostic Mini International Neuropsychiatric Interview, participated. Red cell flux (laser-Doppler flowmetry) was measured during graded intradermal microdialysis perfusion of 5-HT alone (10-10-10-1M) and with the co-perfusion of the NO synthase inhibitor L-NAME (20mM), the SSRI paroxetine (PAX; 10μM), or both. Vascular responsiveness was expressed as a percentage of maximum vascular conductance. Differences between groups and perfusate were analyzed by two-way repeated-measures ANOVA.
Results: 5-HT-induced vasodilation was increased in MDD ($P=0.09$). NO synthase inhibition blunted 5-HT-induced vasodilation to the same extent in both groups (both $P<0.05$). Localized PAX treatment increased 5-HT-induced vasodilation in HC (5-HT=49±13% vs. PAX=62±13%; $P=0.01$), via increased NO-dependent mechanisms (L-NAME+PAX=29±6%; $P<0.01$), but had no effect in MDD (5-HT=74±5% vs. PAX=71±12%; $P=0.99$).
Conclusions: These preliminary data indicate that microvascular sensitivity to exogenous 5-HT is increased in MDD and further suggest that this is not likely mediated via altered NO-dependent or 5-HT reuptake-mediated mechanisms.
Supported By: NIH K99 HL133414
Keywords: Major Depression, Endothelial Function, Serotonin, Nitric Oxide, SSRI

T169. Are Impulsivity and Gene Expression in Postmortem Brains Associated? Preliminary Findings From the Psychological Autopsy Interviews in the UTHealth Brain Collection

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Background: The heterogeneity within psychiatric disorders has complicated the identification of susceptibility genes. One way to address this issue is to explore core characteristics such as 'impulsivity'.

Because impulsivity can also be observed in behaviors, we included as part of our post-mortem study questions about impulsivity for the next of kin in the UTHealth Brain Collection. The current paper presents data regarding reliability of impulsivity ratings and explores the association between impulsivity and gene expression in the prefrontal cortex of cases.
Methods: Postmortem subjects are recruited from the Harris County Institute of Forensic Sciences, Houston, TX, regardless

of the presence of a psychiatric disorder. A psychiatric and psychological assessment is conducted which specifically probes for personality traits in addition to mental health and trauma. We then looked at the association between impulsivity and specific genes identified in a prior genome-wide expression analysis.
Results: Based on joint interviews inter-rater reliability for impulsivity facets was high (ICC $>$ .93). Having a small sample (n $=$9) we explored links to gene expression. Only one of the impulsivity facets was significantly related to MCTS1 [r $=$ -.71)
Conclusions: As far as we know this is this the first study adopting an RDoC approach to assess associations between impulsivity and gene expression in postmortem brain tissue. Most importantly, our results show that these ratings can be reliably assessed. Secondly, keeping in mind the very small sample at this stage, we show that liking gene expression to personality traits in deceased individuals is a promising approach.
Keywords: Impulsivity, Gene Expression, Reliability, Research Domain Criteria (RDoC)

T170. Mental Health and Daily Functioning: Symptom Dimensions and Functional Impairment in an Outpatient Clinic

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Background: The World Health Organization (WHO) estimates that 7.4 % of global disability adjusted life years (DALYs) are caused by mental health disorders. Few outpatient psychiatric clinics administer a standardized assessment and measurement of symptoms and daily functioning on a dimensional scale. We assessed clinical symptoms of anhedonia, depression, anxiety and sleep in an outpatient clinic and the association of these symptoms with every day functioning. We hypothesized that anhedonia would have the strongest association with functional impairment.
Methods: 238 participants filled out the DSM-5 Level 1 Cross Cutting Symptom Measure for adults and the DSM-5 Level 2 measures assessing depression, anxiety and sleep. Question one from the Level 1 Cross Cutting Measure was used to assess anhedonia. The World Health Organization Disability Assessment Schedule 2.0 (WHODAS) was administered to assess overall functioning. Pearson product correlations were run to determine association between functioning levels and symptom severity.
Results: Elevations in all clinical symptoms were significantly correlated with poorer functioning. As hypothesized, anhedonia had the highest positive correlation with overall poor functioning (r$=$ .52, N$=$238) along with anxiety (r$=$ .52, N $=$ 236). This was followed by depressive symptoms (r$=$.44, N$=$238) and sleep problems (r$=$.24, N $=$ 201).
Conclusions: The results highlight the huge impact that clinical psychiatric symptoms have on daily functioning. This provides evidence for the need to create empirically supported interventions that target functioning in addition to clinical symptoms.
Keywords: RDoC, Anhedonia, Daily Functioning, Depression, Anxiety

T171. The Effect of Syndromal and Subthreshold Symptoms of Depression and Mania on Prefrontal and Occipital Cortical Activation During Anticipation of Fear and Neutral Emotional Faces

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Background: Depressed individuals have increased expectation of negative emotional outcomes. Neural correlates of aberrant anticipatory processing in such individuals remain poorly understood. It is even less clear how neural activity related to anticipation of emotional outcomes varies with current depression severity and other mood symptoms.
Methods: We scanned 47 individuals with bipolar disorder, major depressive disorder and healthy controls during anticipation of happy, fearful or neutral faces. We examined relationships among lifetime mania symptoms, current depression severity and anticipatory brain activation for fearful vs. neutral faces.
Results: There was an interaction effect of current depression severity and lifetime mania symptoms on neural activity in the left DLPFC and right occipital cortical regions during anticipation of fearful vs. neutral faces (p-corrected$<$0.05). Across diagnoses, greater DLPFC, but lower occipital cortex activity during anticipation of fearful vs. neutral faces was found in subjects with greater lifetime mania and greater current depression, and those with lower mania and lower depression.
Conclusions: Left DLPFC is a key region for cognitive control, while occipital cortex is involved in visual imagery and processing. Subjects with high lifetime mania and high current depression symptoms may attempt to exhibit cognitive control over potential negative outcomes that they have difficulty imagining or visualizing. Therapeutic interventions, including novel methods of neuromodulation, that target depressive symptoms should consider patients' lifetime experiences with mania symptoms along with current levels of depression. The former maybe a factor that determines the desired direction of neural changes (increase or decrease in activity in a target region).
Supported By: K01MH104348
Keywords: Emotional Anticipation, fMRI, DLPFC, Bipolar Disorder, Depression

T172. Gender-Specific Relationship Between Early Life Stress and Inflammatory Markers

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Background: Reports about relationship between inflammatory markers and early life stress (ELS). have been inconsistent. Gender effect could be one explanation for heterogeneous results. This study was designed to examine the effect of

gender on the relationship between ELS and inflammatory factors.
Methods: 163 females and 89 males participants aged 19-65 years completed the study. History of ELS was assessed by the Childhood Trauma Questionnaire, and participants were divided into ELS and non-ELS groups or divided by gender. Blood samples were collected for measuring inflammatory factors. Age, body mass index, depression, race and employment status were adjusted for all data analysis.
Results: Compared to non-ELS group, tumor necrosis factor-α (TNF-α), but not other inflammatory factors, was significantly elevated in ELS group ($p=0.045$). Comparisons were then performed within genders. The TNF-a levels were much greater in females with ELS compared to females without ELS ($p=0.008$), but not in males with vs. without ELS. Between-gender comparisons in ELS participants revealed that levels of TNF-α, interleukin (IL)-6, IL-10, adiponectin and leptin were significantly greater in females with ELS compared to males with ELS. Differences were not found in other measured factors between females and males with history of ELS. Correlational analysis revealed that IL-6 correlated with emotional abuse and TNF-α correlated with physical abuse in females only.
Conclusions: Our results indicate that the association between ELS and inflammatory factors may hold true, but in females only. Further research is needed to further explore potential mechanisms linking ELS to inflammatory markers in females.
Supported By: NIDDK
Keywords: Early Life Stress, Inflammatory Markers, Gender, Gender Differences

T173. Naturalistic Clinical Monitoring of rTMS-Induced Plasticity With TMS-EEG

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Background: Neurostimulation could be a precise and powerful tool for circuit remediation and clinical treatment. However, TMS treatment parameters are still determined by trial-and-error. Additionally, often biomarkers from small clinical trials with strict inclusion/exclusion criteria do not generalize. We present real-world efforts to incorporate TMS-EEG into the clinic to understand how brain changes relate to treatment parameters, symptoms, and comorbidities.
Methods: Patients meeting criteria for medication-resistant MDD were treated with standard rTMS (daily L-DLPFC, 10Hz for Neuronetics, 18Hz for Brainsway, ~3000 pulses, 4-6 weeks). In addition to clinical assessments (QIDS, GAD7), weekly pre/post treatment single pulse TMS (100 pulses, 3s ISI, 120% MT to L-DLPFC) were applied. Analysis included inter- and intra-session changes in early (10-50ms) and later (50-250ms) TMS-EEG potentials, and a comparison to clinical symptoms.
Results: We report a 95% enrollment, with EEG adding <10 minutes ($N=25$, 5.5 sessions / patient). Clinicians felt the research did not impeded clinical treatment. TMS-EEG were high enough signal-to-noise to measure single subject effects. Qualitatively, for many patients a consistent intra-session effect of left prefrontal TMS-EEG change was observed in the late TEP component. We observed a strong correlation between baseline depressive symptoms and late TEP potential 100-200ms ($N = 25$, $r = 0.65$, $p<.05$ using canonical correlation analysis), with no relationship between early (10-50ms) TEP and depressive symptoms.
Conclusions: It is feasible to incorporate TMS-EEG into a busy clinic and obtain quality measures of brain excitability. Future work will focus on expansion to other hospitals and development of biomarkers that predict and track clinical outcome.
Keywords: TMS-EEG, rTMS, Depression

T174. Neuroanatomical Variation and Associations With Drinking Behavior, Drinking Motives, and Risk-Taking in Young Adults With Bipolar Disorder

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Background: Alcohol use disorders (AUDs) occur at a higher rate in individuals with bipolar disorder than the general population. We previously reported lower gray matter volume (GMV) in several prefrontal regions in adolescents with bipolar disorder who on average six years later reported alcohol use problems, compared to those that did not. How neuroanatomical variation translates into risk is unclear. Therefore, we are now investigating neuroanatomical variation in bipolar disorder and behavioral associations.
Methods: To date, 17 young adults (6 with bipolar disorder and 11 healthy participants) with no prior AUDs (82% female, meanage+stdev= 22+2 years) have completed structural magnetic resonance imaging and a battery of alcohol-related measures including the Daily Drinking Questionnaire, Drinking Motives Questionnaire, and the Iowa Gambling Task (IGT). In this preliminary analysis, we investigated group differences in drinking patterns over the last three months and relationships between drinking patterns and variation in prefrontal cortical GMV within bipolar disorder.
Results: Individuals with bipolar disorder reported greater frequency of drinking ($p=0.02$) but did not differ in quantity consumed or rate (drinks consumed per hour) of drinking. Greater quantity consumed was associated with lower ventral prefrontal GMV while increased rate of drinking was associated with lower rostral and dorsolateral prefrontal GMV ($p<0.005$, >20 voxels). Lower ventral GMV was associated with greater coping motives for drinking while lower rostral and dorsolateral GMV was associated with greater risk-taking on the IGT ($p's<0.05$).
Conclusions: These preliminary results from our ongoing study suggest that variation in prefrontal GMV in bipolar disorder may increase risk of developing AUDs.
Keywords: Bipolar Disorder, Alcohol Use Disorder, Magnetic Resonance Imaging, Risk-Taking, Disease Heterogeneity

T175. Exploring the Synaptic Basis of Rapid Antidepressant Treatments in a Congenital Learned Helplessness Model

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Background: Depression leads to significant impairment in daily function. The prolonged time course necessary for current pharmacological treatment may extend suffering, and increase risk of suicide. Therefore, development of rapid treatments may be helpful by speeding recovery time and reducing suicidality. Two treatments with reproducible clinical efficacy are total sleep deprivation and ketamine administration. Amazingly, these treatments not only alleviate depressive symptoms in refractory patients, but also rapidly reduce suicidality. We used an inbred line of congenital learned helplessness (cLH) rats, a validated model of Major Depressive Disorder (MDD), to examine the synaptic effects of both sleep deprivation and ketamine administration. These rats have a hyperactive lateral habenula (LHb), an epithalamic nucleus that regulates dopamine release from the VTA. Hyperactivity in the habenula leads to decreased dopamine release from the VTA, and depression-like symptoms in these rodents.
Methods: We used a variety of systems neuroscience and molecular biology techniques to examine alterations in habenular signalling resulting from rapid antidepressant treatment. We also employed single molecule imaging techniques to examine changes in neuronal gene expression.
Results: Our results demonstrate both sleep deprivation and ketamine are effective in reducing depression-like symptoms in cLH rats. This response may be mediated by reduced activity in the lateral habenula leading to increased dopaminergic signalling from the VTA.
Conclusions: By gaining a greater understand of the neural circuits involved in rapid antidepressant response we can better adapt these treatments to the clinic, as well as optimize for improved effectiveness.
Supported By: R01-MH091119-07; NIMH; R. Malinow, A Synaptic Locus Controlling Behavioral Depression
R25-MH101072-05; NIMH; N. Swerdlow, Psychiatric Research Residency Training Track
Keywords: Antidepressant Action, Lateral Habenula, Systems Neuroscience

T176. Controllability of Structural Brain Networks in Depressed Patients Receiving Repetitive Transcranial Magnetic Stimulation

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Background: Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (lDLPFC) is an FDA-approved treatment for depression. Increasing evidence indicates that depression is accompanied by altered structural connectivity in the white matter. We investigate the relationship between controllability of structural brain networks and rTMS treatment response.
Methods: The IRB of Weill Cornell Medical College approved this study. 25 currently treatment-resistant depressed patients (age 21−68) received daily 10-Hz rTMS over lDLPFC 5 days/week for 5 weeks. Treatment response was assessed using the 24-item Hamilton Rating Scale for Depression (HAMD-24). Diffusion tensor images were acquired within 7 days prior to and within 3 days after the rTMS treatment course. Global tractography was performed using a spherical convolution model in MRtrix 3. A weighted connectivity matrix was computed based on number of streamlines traversing between 471 subparcellated anatomical brain areas in the Harvard-Oxford atlas. We computed average controllability (ability of a brain region to drive the network into easily-reached states) and modal controllability (ability of a brain region to drive the network into difficult-to-reach states).
Results: At lDLPFC, average controllability at baseline was positively correlated with the change in HAMD-24 from before to after rTMS (Pearson correlation $r = 0.62$, $p < 0.001$). Modal controllability at baseline was negatively correlated with the change in HAMD-24 ($r = 0.-64$, $p < 0.001$) at the lDLPFC and right superior parietal regions.
Conclusions: Our results offer insights into the mechanisms driving brain state transitions in depression. Network controllability could be a useful biomarker of TMS treatment response.
Supported By: NIMH intramural research program
Keywords: Repetitive Transcranial Magnetic Stimulation, Network Analysis, Controllability, Major Depression

T177. Dynamic Temporal Inflexibility of the Frontoparietal Network Predicts Depression Severity and Treatment Response in Internalizing Psychopathologies

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Background: Internalizing psychopathologies (IPs), such as anxiety disorders and depression, are highly comorbid and share neurobiological mechanisms. In IPs, the frontoparietal network (FPN) has been heavily implicated, and FPN regions are common targets of TMS studies. However, how dynamic temporal inflexibility of the FPN contributes to IP symptoms and influences cognitive behavioral therapy (CBT) remains poorly understood. Here we address these questions in two large fMRI resting-state datasets involving treatment-seeking patients with IPs.
Methods: We first performed factor analysis on IP symptom severity scores in the combined datasets (Dataset 1, n=101; Dataset 2, n=102). Resting-state fMRI time-series were extracted from 264 distributed brain nodes, including the FPN. FPN temporal flexibility was assessed by computing the proportion of cross-module interactions over time. Finally, changes in symptom severity were assessed after 12 weeks of CBT.

Results: Factor analysis revealed a five-factor structure representing depression, panic/somatic anxiety, performance/social anxiety, provider-rated symptoms, and non-specific arousal. Temporal flexibility of the FPN negatively correlated with depression in Dataset 1 (r=-.234, p=.018), and in a severity-matched subset of Dataset 2 (n=49; r=-.285, p=.047). Furthermore, increased FPN temporal flexibility was significantly related to depression severity improvement after CBT in Dataset 1 (n=67, r=-.264, p=.031), and showed a similar trend in Dataset 2 (n=20, r=-.297, p=.204).
Conclusions: In two independent samples, we demonstrate that FPN temporal flexibility predicts depression severity and CBT response amongst patients with IP. We suggest that altering aberrant temporal dynamics of the FPN may provide a precise treatment target for depression symptoms in patients with multiple comorbid IPs.
Supported By: R01MH101497, K23MH093679
Keywords: Depression and Anxiety, Resting-State fMRI, Functional Connectivity, Treatment Predictions, Frontoparietal Network

T178. Concomitant Changes in RNA Editing Markers in Brain and Blood of Suicide Attempters

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Background: Altered RNA editing has been associated with neuropsychiatric disorders. Most studies are conducted on small sample size and rely on analysis of brain tissue. We herein investigated possible correlations in RNA editing between brain tissue and blood samples in control and suicide patients.
Methods: RNA was extracted from brain tissue or blood samples from 2 different cohorts. Brain samples of suicide and controls were obtained from the brain collection of Department of Psychiatry, Columbia University. Blood samples were provided by University Hospital, Montpellier (controls, MDD and MDD suicide attempters). Gene expression levels were assessed by qPCR. RNA editing modifications were measured on specific sites by targeted gene sequencing using NGS.
Results: Significant modifications in gene expression of ADARs, the enzymes responsible for RNA editing, were measured in both cohorts in the suicide groups. In parallel, we identified site-specific RNA editing events on phosphodiesterase 8A (PDE8A), which were significantly lower in suicide attempters over and above the deficit observed in MDD. The same changes in (PDE8A) RNA editing were found in brain tissue and blood samples. Longer-term (>1 month) recovery after suicide attempt saw editing levels return to MDD non-suicide attempt levels.
Conclusions: RNA editing is a dynamic process, which can be measured at specific sites to discriminate between suicide, MDD and controls. Our data suggest that some key changes in RNA editing in the brain, which have been hypothesized to participate in the pathophysiology of depression and suicidal behavior, can be detected in blood samples and therefore measured more easily in patients.
Keywords: Epigenetic Biomarkers, Suicide, Human Brain, Human Blood, New Generation Sequencing

T179. Incentive Motivation as Input for Confidence Judgements: Overlap Between Neural Circuits

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Background: Accurately estimating confidence in one's actions is critical to optimize subsequent decisions and increasing evidence suggests that confidence biases could contribute to pathological behavior. We recently showed that monetary incentives bias confidence judgments: gain prospects increase overconfidence while loss prospects decrease overconfidence. Here we investigate the neural basis of this bias, testing the hypothesis that incentive motivation is integrated into confidence judgements via overlapping neural circuits.
Methods: 31 healthy controls completed a perceptual decision task that included incentives and confidence ratings in the fMRI scanner. We modelled the BOLD signal with confidence rating as a parametric regressor at the moment of choice, and incentive conditions as separated events (win/neutral/loss) at moment of rating. The neural overlap between confidence ratings and gain (vs neutral) or loss (vs neutral) was assessed using conjunction tests.
Results: At the behavioral level, we replicated the biasing effect of incentives ($p<0.001$) on confidence. At the neural level, we found a joint positive activation to gain prospects and confidence ratings in the ventral striatum ($p=0.028$). Besides, we found a joint activation to losses and negative confidence ratings in the anterior cingulate cortex ($p=0.006$) and right insula ($p=0.022$).
Conclusions: The co-involvement of these regions in value and confidence processing may underlie the biasing effect of incentives on confidence. This biasing effect could contribute to suboptimal decision-making in the face of monetary gains as observed in pathological gambling.
Supported By: Amsterdam brain and cognition (ABC)
Keywords: Confidence, Pathological Gambling, Incentive Motivation, Decision Making

T180. Unraveling the Effect of Physiological Stress on Chaperone Mediated Autophagy-Dependent Synaptic Proteostasis

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Background: Protein turnover is fundamental for correct neuronal and synaptic functioning. It is assessed that

physiological stress has a major impact on neuronal connections and synaptic plasticity. With this study we investigate the effect of physiological stress on neuronal proteostasis (protein homeostasis). Knowing that stress regulates the expression of several chaperones, we focused our study on the mechanism of chaperone mediated autophagy (CMA) and on the HSP90 co-chaperone FKBP51, a key regulator of the stress-hormone axis.

Methods: We generated FKBP51 knock out (KO) cells from the human neuroblastoma cell line, SH-SY5Y using CRISPR-Cas9. Dexamethasone (dex), a synthetic glucocorticoid receptor agonist, was used to mimic acute physiological stress. Knock down (KD) of LAMP2a, the key regulator of CMA, was performed to block CMA. Pulse-chase experiments were performed using Halo-Tag labeled CMA target-proteins to assess the half-life in different conditions.

Results: Pulse-chase experiments in SH-SY5Y FKBP51 KO cells revealed a significantly increased half-life and thus stability of known CMA targets. Similar results were observed in in LAMP2a KD cells, validating the specificity to CMA. In accordance with these findings, we observed a higher degradation rate of CMA targets after treatment with dex, which increases FKBP51 expression. Furthermore, Mass Spectrometry data identified novel FKBP51-dependent CMA targets with relevance to synaptic plasticity.

Conclusions: With this study we characterized for the first time the effect of physiological stress on neuronal protein turnover via CMA. Moreover, we identified novel CMA target proteins highlighting the impact of stress on synaptic proteostasis.

Supported By: funded by a NARSAD Young Investigator Award by Brain and Behavior Research Foundation, honored by P&S Fund (Awarded to Nils C Gassen, Grant ID 25348); Research grant by Boehringer-Ingelheim

Keywords: Chaperon Mediated Autophagy, Stress, FKBP5, Neuronal Proteostasis

T181. LSD Increases Social Adaptation to Opinions Similar to One's Own

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Background: Inferring value from the reactions of others and adapting one's behavior to a social group norm is an essential process in every-day decision making. However, the neuropharmacology of social influence processing is mostly unknown, although lysergic acid diethylamide (LSD), acting at multiple 5-HT2 receptors, has recently been shown to alter social perception.

Methods: The role of the 5-HT2A receptor on social influence on aesthetic judgements was investigated by assessing social feedback processing and subsequent decision making in 23 healthy participants via fMRI and behavioral ratings. Participants received 1) placebo+placebo, 2) placebo+LSD (100 μg po), or 3) ketanserin - a selective 5-HT2A receptor antagonist (40 mg po)+LSD in three different sessions.

Results: Participants adapted their opinion more strongly to the group norm in the high conflict (HC) condition than the low conflict (LC) condition under placebo and ketanserin+LSD. This pattern was reversed by LSD (all $p<0.05$, Bonferroni corrected). Processing LC was associated with increased BOLD signal in the dorsal striatum in the LSD condition, while processing HC was associated with increased BOLD signal in the supplementary motor area in the placebo condition. No differences in BOLD signal were observed during decision making.

Conclusions: LSD increases adaptation to opinions similar to one's own, presumably via stimulation of 5-HT2A receptors. FMRI results reveal that this is rather attributable to alterations in social feedback processing than to decision making. The data shed light on the role of the 5-HT system in social influence processing and are important for the development of novel treatments in psychiatric disorders.

Supported By: Heffter Research Center

Keywords: Serotonin 2A Receptor, Social Cognition, BOLD fMRI, Pharmacology, Psychedelic

T182. GABA and Glutamate in Patients With 22q11.2 Deletion Syndrome and Healthy Volunteers and the Relation With Cognition: A Randomized Double-Blind 7Tesla Pharmacological MRS Study

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Background: One of the genes located in the deleted region of patients with 22q11.2 deletion syndrome (22q11DS) is PRODH which is involved in glutamate (GLU) neurotransmission. With this study we aimed to investigate GLUergic and GABAergic reactivity in the anterior cingulate cortex (ACC) and striatum in medication-free patients with 22q11DS and controls.

Methods: 12 22q11DS (mean age 35 years) patients and 20 controls (mean age 31 years) were enrolled in the study. ACC and striatal GABA and GLU levels were obtained both after placebo and after 50 mg. riluzole (agent with anti-glutamate and pro-GABA action) using 7Tesla Magnetic Resonance Spectroscopy (MRS). Within the 22q11DS group, the relationship between cognition and GABA and GLU levels were examined.

Results: After placebo, ACC and striatal GLU and GABA levels did not differ between the 22q11DS and control group. A trend level significant increase in striatal GABA concentrations was found after riluzole ($p= 0.065$). No other main or interaction effects were found. ACC GLU levels correlated inversely with verbal memory ($p= 0.030$) and attention ($p= 0.010$). Attention correlated significantly with ACC GABA levels ($p=0.024$). A positive correlation was found between visual memory and striatal GLU levels ($p=0.043$).

Conclusions: Current results did not demonstrate differences in ACC and striatal GLU and GABA levels, nor in GLUergic or GABAergic reactivity in response to riluzole between 22q11DS and controls. These results suggest a role for GLU and GABA in cognition in the 22q11DS group. Therefore, influencing these neurotransmitter systems might enhance cognitive functioning in these patients.
Supported By: SWOL
Keywords: 22q11 Deletion Syndrome, Magnetic Resonance Spectroscopy, Neurocognition, Glutamate, GABA

T183. Gender Differences in Seropositivity and Metabolic Associations of Toxoplasma Gondii Oocyst IgG in the Old Order Amish

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Background: Toxoplasma gondii (T.gondii) has been associated with mental illness, suicidal behavior and "infectobesity". Foodborne infection with T.gondii is common and occurs either through the ingestion of oocysts (originating in cat feces contaminating soil, vegetables and water) or of tissue cysts (ingested with undercooked meat). The oocyst is capable of surviving harsh conditions and most common methods of disinfection. We have previously reported a high seroprevalence and familial aggregation of T. gondii infection, and marked gender differences in risk factors. We now focus on oocyst IgG seropositivity.
Methods: We analyzed 1647 participants recruited from the Amish Wellness Study, with mean (SD) age of 42.4 (17.0) with 61.4% women. T. Gondii IgG anti-oocyst antibodies were measured using ELISA, seropositivity calculated, and related, using multivariable linear and logistic models with adjustment for age and stratification by gender, and further adjustment for neopterin as a biomarker for inflammation.
Results: Oocyst positivity was more common (65% of T.gondii positives) than non-oocyst seropositivity. In men, oocyst seropositivity was higher and associated with systolic blood pressure ($p=0.002$), and LDL ($p=0.031$) with loss of significance after adjusting for log neopterin. In women, associations between oocyst positivity and obese/ overweight status ($p= 0.038$) and systolic blood pressure ($p=0.010$) emerged as significant only after adjustment for log neopterin.
Conclusions: We report a high anti-oocyst seroprevalence, associated with certain metabolic syndrome components, thus potentially elevating cardiovascular risk. While immune activation may mediate in part these associations in men, they appear to confound them in women.
Supported By: University of Maryland, Joint Institute for Food Safety and the Applied Nutrition JIFSAN/ FDA cooperative agreement FDU.001418; NORC exploratory grant (PI Postolache), offspring of the parent grant P30 DK072488
Keywords: Toxoplasma Gondii, Oocysts, Mental Illnesses, Old Order Amish, Metabolic Syndrome

T184. Effects of Pregnenolone Administration on Emotion Regulation Neurocircuits in Trauma Brain Injury

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Background: Mild TBI is associated with emotional dysregulation, but there are no approved treatments targeting emotional regulation. Oral neurosteroid supplementation has anxiolytic effects that lead to changes in brain activity in emotion regulation regions: right insula, right amygdala and dorsal medial prefrontal cortex (dmPFC). We conducted an 8 week RCT of pregnenolone in mild TBI patients to assess changes in emotion regulation circuits through functional magnetic resonance imaging (fMRI).
Methods: Twenty-six veterans of mild TBI per ACRM criteria were administrated a two-week single blind placebo lead-in followed by eight weeks of treatment randomized to adjunctive pregnenolone ($N=16$) or placebo ($N=10$). Participants were scanned during the Shifted-attention Emotional Appraisal Task at trial-week 4 and 12, respectively. Brain activations from insula, amygdala and dmPFC were analyzed using an ANOVA model with factors for TREATMENT (pregnenolone and placebo), VALENCE (fearful and neutral) and TIME (pre-treatment, post-treatment).
Results: Fearful versus neutral facial expression elicited stronger insula activation at post- compared to pre-treatment in the pregnenolone group ($t(15)=2.057$, $p=0.058$; trend significance) but not in placebo group ($t(9)=-1.020$, $p=0.335$). No significant treatment effects were detected in amygdala or medial prefrontal cortex.
Conclusions: Eight weeks of oral pregnenolone is associated with greater right insula activation than placebo, suggesting that pregnenolone may have a role in emotion regulation in veterans with mild TBI. Adjunctive pregnenolone treatment offers a new therapeutic possibility to address emotional lability in veterans with mild TBI pending validation in a larger sample size.
Supported By: This project was supported in part by the Department of Veterans Affairs' (VA) Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC) of the VA Office of Mental Health Services, the Mid-Atlantic Healthcare Network, and the Office of Research and Development (ORD; 5I01CX000748-01, 5I01CX000120-02). Additional financial support was provided by VA Merit Review, RR&D (5I01RX000571; Dr. Marx) and the National Institute for Neurological Disorders and Stroke (R01NS086885-01A1; Dr. Morey). Dr. Naylor was supported by a VA Career

Development Award (1IK2RX000908) from the Rehabilitation Research and Development (RR&D).
Keywords: fMRI, Mild Traumatic Brain Injury, Insula, Emotion Regulation, Allopregnanolone

T185. Electrophysiological Evidence of Auditory Habituation Abnormalities in Young Adults With Phelan-Mcdermid Syndrome

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Background: Phelan-McDermid Syndrome (PMS) is a rare disorder involving a mutation or deletion in the SHANK3 gene that affects synaptic and glutametergic function. PMS is characterized by global developmental delay, including intellectual disability, delayed or absent speech, and hypotonia. It confers high risk for autism spectrum disorder (ASD), and mood disorders often emerge during adolescence. Based on observations of sensory hyporeactivity in individuals with PMS, we hypothesize that cortical response to auditory stimuli will be reduced, whereas habituation will be enhanced in this population.
Methods: EEG was recorded from 6 individuals with PMS (aged 13-18) and 7 healthy controls (aged 14-32) while a series of four consecutive 1000Hz tones was repeatedly presented. Within trials, each tone was separated by 500ms; inter-trial interval was 4000ms. Amplitudes of N1 and P2 event-related potentials (ERP) were extracted and compared between groups.
Results: Compared to controls, the PMS group displayed a marked decrease in P2 amplitude to the initial tone (d=.932) and stronger P2 habituation (d=.720) when comparing the amplitude ratio between tones 1 and 4. N1 response to the initial tone and N1 habituation did not differ between groups.
Conclusions: Our findings reveal a trend towards cortical hyporesponsiveness and more pronounced habituation to auditory stimuli in PMS. These results are consistent with behavioral observations in this disorder. Electrophysiological response during auditory habituation may offer a promising biomarker for use in measuring treatment effectiveness, as well as reveal underlying neural dysfunction in this neurodevelopmental disorder.
Supported By: U54
Keywords: Electroencephalography (EEG), Phelan-McDermid Syndrome, Auditory Perception

T186. Perceptual and Executive Behavioral Deficits in ADHD and Their Differential Correlation With Microsaccade Rate

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Background: While executive function and attention have been extensively studied in ADHD, perceptual function has received less scrutiny. Additionally, in prior studies, stimulus encoding/processing (perceptual function) have been intertwined with response selection (executive function). We utilized a novel task to dissociate these functions.
Methods: We parametrically varied low-level stimulus features (orientation and color), providing a fine-grained analysis of perceptual function. In half of the blocks, participants were also required to switch their attention between feature dimensions on a trial-by-trial basis (assessment of executive processes). 20 ADHD participants and 20 Controls performed this task, with half of the participants in each group eye-tracked. Our response paradigm also captured task-irrelevant motor output (TIMO), reflecting failures to use the correct stimulus-response rule.
Results: ADHD patients had worse perceptual function and higher TIMO than Controls. Based on perceptual variability alone, we were able to classify participants into ADHD and Controls with a mean accuracy of about 77% (Mihali, Young et al, submitted). Across all participants the perceptual variability parameter was correlated with TIMO ($\rho = 0.41$, $p = 0.0085$). Within the eye-tracked participants we found a differential correlation of microsaccade rate (suppressed around stimulus onset to facilitate perceptual encoding) with perceptual variability ($\rho = 0.65$, $p = 0.002$), but not with TIMO ($\rho = 0.23$, $p = 0.33$).
Conclusions: Our results highlight the role of perceptual variability in ADHD and its usefulness towards diagnosis. The differential correlation with microsaccades suggests that our two task metrics seem to reflect distinct neural processes (though likely reliant on partially overlapping circuits).
Supported By: ARSF53101, R01EY020958
Keywords: Psychophysics, ADHD, Microsaccades, Perceptual Variability, Task Switching

T187. Transcranial Direct Current Stimulation (tDCS) for the Affective Symptoms of Chronic Low Back Pain (CLBP): A Double-Blinded, Randomized, Placebo-Controlled Trial

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Background: "Pain" has sensory and affective (emotional) components. CLBP's affective symptoms underlie associated disability and psychiatric comorbidity and have limited treatments (e.g. cognitive behavioral therapy); consequently, there is over-reliance on opioid analgesics with deleterious side effects. tDCS may noninvasively modulate pain-related affective distress. We present full analysis of a first multi-site,

double-blinded, randomized placebo-controlled trial (RCT) of tDCS targeting left dorsal anterior cingulate cortex, a region implicated in pain's affective component, in CLBP patients.
Methods: Twenty-one participants completed the study. Carbon-rubber electrodes within 5x7 cm saline-saturated sponges were placed over FC1 (10-20 EEG coordinates) and the contralateral mastoid. We adapted this empirically-based montage from our prior work and verified it with post-hoc electric-field modeling. Participants received 10 daily sessions of sham or active tDCS (20 minutes/session, 2mA, cathodal polarity relative to return electrode) and rated pain-related intensity (DVPRS), acceptance (CPAQ-8), interference (WHYMPI General Activity Subscale), disability (RMDQ), and anxiety (PASS-20), as well as depression (PHQ-9).
Results: Regression analysis noted significantly improved WHYMPI General Activity ($p=0.002$), RMDQ ($p=0.001$), and PHQ-9 ($p=0.003$) scores at 6-week follow up with active vs. sham tDCS. Although not statistically significant, active tDCS had medium effects for Day 1 ($|d|=0.49$) and 10 ($|d|=0.35$) CPAQ-8. Participants prescribed opioids had significantly lower Day 1 CPAQ-8 ($p<0.001$) than non-opioid participants.
Conclusions: Participants who received active tDCS showed improvements in pain disability and depression. Future studies would benefit from larger double-blinded RCTs to increase power.
Supported By: 2015 NARSAD Young Investigator Grant, NIMH R25 MH101076
Keywords: Transcranial Direct Current Stimulation (tDCS), Chronic Low Back Pain, Dorsal Anterior Cingulate Cortex, dACC, Noninvasive Brain Stimulation

T188. Ceramide Accumulation is Associated With Declining Verbal Memory in Coronary Artery Disease Patients

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Background: Biomarkers in cognitively vulnerable populations like those with coronary artery disease (CAD) may inform earlier intervention in vascular neurodegeneration. Circulating ceramide C18:0 (CerC18:0) is associated with changes in verbal memory in early neurodegeneration and CAD progression. We hypothesized that plasma CerC18:0 and its accumulation in biosynthesis pathways (catabolism of sphingomyelin (SM), salvage from monohexosylceramides (MHx), formation from sphingosine-1-phosphate (S1P)) would be associated with declining verbal memory performance in CAD.
Methods: In addition to analyzing total CerC18:0, CerC18:0 ratios assessed CerC18:0 accumulation: CerC18:0/SM18:0, CerC18:0/MHx18:0, and CerC18:0/S1P in the catabolic, salvage, and recycling pathway, respectively. Verbal memory was assessed using the California Verbal Learning Test. Using mixed models in 59 CAD participants, we evaluated associations between baseline CerC18:0 ratios and changes in verbal memory, adjusting for age, body-mass index, and education. Given that cognitive decline is more rapid following onset of deficits, sub-analyses were conducted in participants with possible vascular mild cognitive impairment (VaMCI).
Results: Increased baseline CerC18:0 (b[SE]=-0.83[0.31], $p=0.01$) was correlated with worse verbal memory performance over time. Increased baseline CerC18:0/SM18:0 (b[SE]=-4.43[1.61], $p=0.01$) and CerC18:0/MHx18:0 [(b[SE]=-0.67[0.32], $p=0.04$)] were also correlated with worse verbal memory over time. In sub-analyses of CerC18:0/SM18:0, this relationship was maintained only in those with possible VaMCI ($n=14$) at baseline [(b[SE]=-6.25[2.60], $p=0.04$)].
Conclusions: These findings support aberrant CerC18:0 metabolism as an early neurobiological change in vascular neurodegeneration and invite further research to determine whether its pathways may be a clinically relevant target for drug discovery. Future studies should measure enzymes responsible for conversion of precursors into CerC18:0 to assess enzymatic activity.
Supported By: Canadian Institute of Health Research
Keywords: Vascular Cognitive Impairment, Coronary Artery Disease, Ceramides, Verbal Memory

T189. Biomarker Prediction of Psychotherapy Outcomes in Borderline Personality Disorder: Systematic Review

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Background: Borderline personality disorder (BPD) is associated with severe functional impairment and high suicide risk (Leichsenring et al., 2011), with neurobiological mechanisms implicated in Aetiology and maintenance of the disorder (Ruocco et al., 2016). Psychotherapy is an evidence-based treatment (Cristea et al., 2017) and the discovery of biomarkers may enhance treatment and prevention efforts (Abi-Dargham et al., 2016). This systematic review investigates pretreatment biomarkers that predict psychotherapy outcomes in BPD or change following psychotherapy.
Methods: Studies published until April 2017 were selected after searching PsycINFO, PubMed/MEDLINE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Search terms encompassed evidence-based psychotherapy interventions for BPD keywords, neurobiological marker keywords, and BPD diagnosis keywords.
Results: Thirteen studies were included (neuroimaging: $n = 10$, genetics: $n = 2$, other: $n = 1$). Higher prefrontal and cingulate cortex and reduced limbic activation after psychotherapy were identified via neuroimaging methods utilising various affective stimuli. Clinical improvement was predicted

by both activation and hypoactivation of areas mainly within these regions. Studies were characterised by diverse methods of treatment delivery, biomarker measurement, and definitions of treatment response, suggesting the field is in an early developmental stage.
Conclusions: The discovery of biomarkers will assist in predicting treatment response and unravelling the mechanisms of psychotherapy. Future replication and large-scale exploratory studies in BPD are required. Clinical translation of these findings may promote prevention, greater diagnostic clarity, personalised treatment selection, improved treatment response rates, and aid the evolution of psychiatric nosology more broadly to move beyond symptom-based classification.
Keywords: Borderline Personality Disorder, Biomarkers, Treatment Response, Psychotherapy, Neuroimaging

T190. Incision Pain in Patients With Borderline Personality Disorder (BPD) With Current or Past Use of Non-suicidal Self-Injury

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Background: The aim of this study was to scrutinize painfulness after stress induction and incision or sharp mechanical pain without tissue damage in BPD with current NSSI with skin lesion in the last six months (NSSI-current) and past NSSI with skin lesion in the past (NSSI-past).
Methods: We included three female groups: 57 NSSI-current, 30 NSSI-past and 60 female healthy controls (HC).

After a stress induction, one of the following stimuli was applied to the volar forearm: an incision with a scalpel, a blade stimulator (blunt blade with no skin lesion), or a touch. 45minutes after stress induction and stimulation mechanical pain thresholds (MPT) and mechanical pain sensitivity (MPS) were measured with different pinpricks in a repeated increasing and decreasing order. All participants rated sensory and affective components of pain on the SES-scale (Schmerzempfindungsskala).
Results: MPT were not different between the groups for all three stimuli. There were significantly higher MPS ratings in HC compared to NSSI-current and NSSI-past for the stimuli incision and blade ($p<0.05$). Affective components of pain were higher in HC than in patients ($p<0.05$), but not in sensory components. NSSI-current and NSSI-past did not differ in any variable.
Conclusions: Affective ratings of pain are reduced in NSSI-patients and may be a key factor of the overall lowered perception of pain. The sensory system in NSSI-patients is apparently not impaired. In contrast, the processing of affective-cognitive component of pain appears to be altered in NSSI-patients. The blade stimulator can be used as a surrogate for incision in NSSI-current and NSSI-past.
Supported By: Supported by the German Research Foundation (DFG; KFO 256, SCHM 1526/15-1, TR 236/20-1).

Keywords: Non-Suicidal Self-Injury, New Surrogate for Incision Pain, Sensory and Affective Components of Pain, Borderline Personality Disorder, Mechanical and Incision Pain

T191. Sex Differences in Psychopathy Predict Physical, Verbal, and Indirect Aggression

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Background: Psychopathy is a multidimensional construct, considered one of the best predictors of aggression and violent behavior; however, most studies have been conducted with prisoners and our understanding of the relationship between psychopathy and aggression in community samples remains limited. Further, although psychopathy is one of the most frequently researched predictors of aggression, there is a scarcity of studies exploring differences between men and women. The goal of the present study was to understand what facets of psychopathy predict different forms of aggression in men and women.
Methods: We administered the four facet Psychopathy Checklist: Screening Version (PCL:SV) and the Buss Warren Aggression Questionnaire to a large Bulgarian community sample (N=565) of 385 men and 180 women. Hierarchical linear regressions, which included Antisocial Personality Disorder and Substance Use Disorder as covariates, examined the utility of the four facets of psychopathy to predict verbal, physical, and indirect aggression in men and women.
Results: Results revealed that physical aggression was predicted by affective and antisocial psychopathic traits, verbal aggression was predicted by the interpersonal and antisocial facets, and indirect aggression was predicted by the antisocial facet of psychopathy. Sex significantly moderated the association among facets of psychopathy and physical and indirect aggression. Specifically, the affective facet was positively associated with physical aggression only for women, whereas the antisocial facet was positively associated with indirect aggression only for men.
Conclusions: Results suggest that the four-facet model is sensitive to capture important similarities and differences between males and females when predicting forms of aggression.
Supported By: R01DA021421 (JV) by NIDA and Fogarty International Center
Keywords: Gender Differences, Psychopathy, Aggression

T192. Weighted Gene Coexpression Network Analysis of IPSC Generated From Patients With Schizophrenia

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Background: Human induced pluripotent stem cells (hiPSC) have provided a new way of studying Schizophrenia (SZ), by allowing the establishment of cellular models accounting for the patient genetic background. Here we conducted an exploratory RNA-sequencing profiling study of different cell lines derived from hiPSCs generated from somatic cells of subjects from the population isolate of the Central Valley of Costa Rica (CVCR)
Methods: Lymphoblastoid cells lines (LCLs) were transformed into hiPSCs, Neuronal

Precursors Cells (NPC) and cortical neurons, using well establish methodology. RNA from these cells were then sequenced using Illumina HiSeqTM2500. Raw count data measured 48162 transcripts across all samples. The 15000 more expressed genes were subjected to VOOM normalization in EdgeR, a variance-stabilization transformation method. Normalized values were used as input for weighted gene coexpression network analysis (WGCNA). Differential expression of MEs (module eigengene) comparing healthy controls and patients with schizophrenia across all cell types were performed.
Results: On total 4 cell lines (LCL, hiPSC, NPC and cortical neurons) of 6 healthy controls (HC) and 7 SZ patients from the CVCR were included on the WGCNA analysis. Biweight mid-correlation was used to define the coexpression similarity, resulting in 129 modules. Differential expression of MEs were observed on relation to phenotype ($p=0.04$) and presence of NRG1 Val66p.Leu mutation ($p=0.02$). Noteworthy, MEs were able to separate members of the same family from other subjects ($p=0.0006$).
Conclusions: Our study used WGCNA to establish blocks of gene expression on a hiPSC cellular model of SZ related to phenotype and genotype.
Supported By: UTBRAIN Seed Award
Keywords: hiPSCs-derived Neurons, Schizophrenia, WGCNA

T193. Shared Co-Expression Networks in Frontal Cortex of the Normal Aged Brain and Schizophrenia

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Background: Previous studies on the brain of people with schizophrenia have identified structural changes and gene expression changes that suggest that brain aging maybe accelerated in people with schizophrenia.
Methods: To better characterize gene expression profiles in schizophrenia and in the aged population we constructed co-expression networks using RNA-Seq data from frontal cortex. We analysed data from 62 subjects with schizophrenia and 51 unaffected controls ranging in age from 19 to 63 years. We then analysed a separate data set from 114 normal control individuals ranging in age from 29 to 106 years.
Results: In the first data set we found two co-expression modules significantly associated with schizophrenia. One was a downregulated co-expression module enriched for neuron function related genes and the other was an upregulated immune/inflammation-related module. In the second data set of normal individuals, we found 10 co-expression modules significantly correlated with age and identified two that significantly overlapped the two modules associated with schizophrenia. Both neuron-related modules were significantly enriched with genes associated with both pyramidal neurons and GABAergic neurons. Both immune/inflammation related modules were highly enriched with endothelial cell genes and genes associated with activated microglia.
Conclusions: The results indicate that a module related to neuronal function is downregulated and an immune/inflammation related co-expression network may be upregulated in the cells of the blood vessels in both schizophrenia and during normal aging. This finding adds further support to the hypothesis that there may be accelerated brain aging in schizophrenia.
Keywords: RNA-seq, Schizophrenia, Aging

T194. Evaluating the Effects of Antipsychotics on Human Oligodendrocytes by Proteomic Analysis

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Background: Schizophrenia is a severe psychiatric illness that affects millions of people globally, generates large health expenses and deprives patients of a normal life. The diagnosis is clinical and the only way of managing the symptoms is using psychosocial interventions and antipsychotic drugs, which have negative side effects. These drugs are classified into two categories: typical (first-generation) and atypical (second-generation), and its combination with D-serine (an endogenous glutamatergic N-methyl-D-aspartate (NMDA) receptor co-agonist) seems to improve the relief of symptoms. Proteomic studies have associated the development and establishment of schizophrenia to dysfunctions in neurotransmitter systems and oligodendrocytes. The dysfunction of these cells may lead to disturbances in myelination, and consequently to a poor propagation of nerve impulses, compromising cognitive, neural and glial functions. In this context, this project aims to identify the proteins and pathways affected in MO3.13 (a human oligodendrocyte lineage) by the use of haloperidol (first-generation antipsychotic), clozapine (second-generation antipsychotic) and D-serine, through total proteome analyses.
Methods: The proteome characterization will be performed by liquid nanocromatography coupled to mass spectrometry. The MS and MS/MS spectra will be processed using dedicated algorithms in a database search and processing software. The identified and differentially expressed proteins will be categorized into functional classes and analyzed through softwares available online to identify affected pathways and interactomes.
Results: The results obtained will be shown at the time of presentation, and compared with previous findings in samples of patients, aiming to contribute to the understanding of biochemical and molecular mechanisms involved in the action of these drugs.
Conclusions: N/A
Supported By: CAPES
Keywords: Schizophrenia, MO3.13, Mass Spectrometry, Clozapine, Haloperidol

T195. Deficits in Mitochondrial Complex I in Schizophrenia: A Possible Link to Pseudogene Regulation

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Background: Mitochondrial complex I (CoI) deficit, associated with alterations in mitochondrial and neuronal differentiation has been consistently observed in schizophrenia. We aimed to unravel the mechanism that underlies CoI homeostasis defects.
Methods: EBV transformed B lymphocyte lines were analyzed for CI-driven respiration, CoI synthesis and degradation rate, in-gel activity and levels. Import, transcripts sequence and expression of several CoI subunits were analyzed.
Results: CoI-driven respiration deficits were associated with reduced in-gel activity of isolated holo-CoI, CoI synthesis and degradation rates and levels of its labile subunits in patients. Import into mitochondria of NDUFV2, the most affected subunit in schizophrenia, was impaired in patients, due to both protein and mitochondria source (patients or controls). Despite the above deficits, CoI and CoI-bound NDUFV2 levels were normal. This discrepancy probably stems from decreased degradation rate of NDUFV2. To study the mechanism responsible for NDUFV2 deficits we studied its transcription, as deduced from the import study. While transcript sequence was similar in both cohorts, a mix of products was observed in schizophrenia, suggesting interference with the reverse transcriptase. NDUFV2 has a pseudogene (NDUFV2P1), which is an attractive candidate for the regulation of transcription. Indeed, NDUFV2P1 transcript levels were significantly increased in both lymphoblast and frontal cortex specimens in patients, which showed a significant inverse correlation with NDUFV2 pre-protein levels and cell respiration.
Conclusions: Increased NDUFV2P1 transcripts can interfere with NDUFV2 reverse transcription, translation and import, leading to changes in synthesis and degradation rates and activity of CoI and ultimately to mitochondrial dysfunction in schizophrenia.
Supported By: The Israel Science Foundation-ISF (1295/11 and 1517/15)
Keywords: Mitochondria, Complex I, NDUFV2, NDUFV2 Pseudogene (NDUFV2P1), Schizophrenia

T196. Oligodendrocytes Derived From IPS Cells From Subjects With Schizophrenic Disorders are Reduced in Number and Their Number Correlates With in Vivo Myelin Estimated by MTR Brain Imaging

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Background: There is consistent evidence of abnormalities of connectivity and signal transduction in individuals with Schizophrenias (SZ) and Schizoaffective Disorders (SZA). Relevant to those findings, there is convergent in vivo, post mortem, and genomic evidence of abnormal oligodendrocyte development and function and diffusely lower myelination of neurons in brain in SZ, SZA.

We hypothesized that the previously observed disease related variants and abnormal expression levels of myelination pathway genes will produce abnormal outgrowth, migration and myelination capacity in vitro of oligodendrocytes derived from iPS cells from our patients with SZ and SZA, and that these in vitro abnormalities will correlate with measures of white matter integrity and myelination in the same patients studied in vivo with DTS/MTR brain imaging.
Methods: Six Control and 6 SZ, SZA iPS lines, from subjects in our well characterized patient sample were differentiated into oligodendrocytes. FACS analysis of O4 was done at D85 to quantify the number of late Oligodendrocyte Precursor Cells (OPCs) in each line.
Results: A significantly lower number of O4 positive cells was seen in cases (SZ, SZA) vs controls, (t-test $p<0.01$, one-tailed) at D85 when cells are mature and expressing O4 and myelin basic protein (MBP). A significant correlation between MTR brain imaging values for myelin in core white matter and number of O4 positive cells produced at the D85 time point (Pearson $r=0.4975$; $p<0.005$; two −tailed) was also seen.
Conclusions: Reduction in number of OPCs may play a role in the mechanism underlying white matter reduction in SZ.
Supported By: Program for Neuropsychiatric Research-McLean Hospital
Keywords: Oligodendrocytes, Schizophrenia, Schizoaffective Disorder, Human Neural Stem Cells

T197. Isoform and Protein Region Abnormalities of Dysbindin and Copper Transporters in Postmortem Schizophrenia Substantia Nigra

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Background: Dysbindin is downregulated in several regions of the brain in schizophrenia and is suspected to be involved in the cognitive deficits of the disease. Dysbindin plays a role in modulation of the copper transport required for myelination and monoamine metabolism. Since the substantia nigra exhibits one of the highest copper contents of the human brain, we studied this region using Western blot analysis.
Methods: Using Western blot analysis, we characterized differential protein segments of the copper transporters ATP7A and CTR1, as well as ATP7A homolog ATP7B and dysbindin isoforms 1A and 1B/C in postmortem substantia nigra in schizophrenia subjects ($n=15$) and matched controls ($n=11$). We also examined medication status in medicated ($n=11$) versus unmedicated schizophrenia subjects ($n=4$) as a preliminary investigation.
Results: The combined schizophrenia group exhibited increased levels of C-terminus, but not the N-terminus, ATP7A (18.5% increase). Schizophrenia subjects expressed less

transmembrane CTR1 (42.6% decrease) and dysbindin 1B/C (18.8% decrease) than controls. When subdivided by medication status, the increased C-terminus ATP7A protein was present only in medicated subjects (13.5% increase) when compared to controls. Unmedicated subjects exhibited significantly less N-terminus ATP7A protein than controls (35.3% decrease) and medicated subjects (38.3% decrease), suggesting medication-induced rescue of the ATP7A N-terminus. The decrease of transmembrane CTR1 was similar in both treatment groups versus controls, suggesting no medication effect.
Conclusions: These results provide the first evidence of disrupted copper transport into and within schizophrenia nigral cells that may be modulated by specific dysbindin isoforms and antipsychotic treatment, and could reveal new treatment pathways.
Supported By: National Institute of Mental Health R0166123 and R21MH108867; National Institute of Neurological Disorders and Stroke F99NS105208
Keywords: Schizophrenia, Copper, Dysbindin

T198. A Schizophrenia-Associated Missense Mutation in Kalirin Alters Pyramidal Cell Morphology in a Mouse Model

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Background: Kalirin (KAL) is a Rho GEF that is involved in regulation of dendritic morphology. A missense mutation (KAL-PT) has been associated with schizophrenia. KAL coordinates RhoA activation downstream of p75 when p75 interacts with Nogo receptor (NGR). This NGR/p75/KAL complex acts to restrict dendritic morphogenesis. I have found that KAL-PT increases RhoA activity when expressed in vitro and impairs dendritic morphogenesis. We hypothesize that enhanced activation of the NGR/p75/KAL pathway downregulates the expression of microtubule transport proteins and subsequently impairs dendritic morphogenesis across development.
Methods: A mouse model of the KAL-PT mutation was created using CRISPR/Cas9 genome editing. Cortical homogenate was collected from wild-type (KAL-WT) and KAL-PT mice and RNAseq was performed. Differential gene expression and pathway analysis was performed. In vitro morphological studies were performed on DIV8 neurons grown from dissociated cortical cultures derived from KAL-WT, KAL9 heterozygous (KAL-het), and KAL-PT P0 mouse pups, followed by Sholl analysis.
Results: Sequencing data from KAL-PT mice show significant overlap with an existing dataset generated from Nogo-B overexpression with enrichment for downregulation of microtubule transport molecules. In vitro studies demonstrate decreased dendritic branching and length in pyramidal neurons from KAL-PT cortical cultures compared to KAL-WT.
Conclusions: The PT mutation results in perturbation of signaling to the cytoskeleton, with enrichment for disruptions in microtubule transport proteins. These signaling pathway perturbations may underlie the decreased dendritic length and complexity observed in pyramidal cells in schizophrenia. Using a disease-associated mutation to model convergent pathway perturbations involved in cytoskeleton remodeling may aid the development of novel pharmacotherapeutics for schizophrenia.
Supported By: MH071533
Keywords: Schizophrenia, Kalirin, Dendrite

T199. Leukocyte Mitochondrial DNA Copy Number in Schizophrenia

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Background: Schizophrenia is a complex neuropsychiatric disorder with significant genetic predisposition. In a subset of schizophrenia patients, mitochondrial dysfunction could be explained by the genomic defects like mitochondrial DNA Copy Number Variations, which are considered as a sensitive index of cellular oxidative stress. Given the high energy demands for neuronal functions, altered Mitochondrial DNA copy number (mtDNAcn) and consequent impaired mitochondrial physiology would significantly influence schizophrenia pathogenesis. In this context, we have made an attempt to study mitochondrial dysfunction in schizophrenia by assessing mtDNAcn in antipsychotic-naïve/free schizophrenia patients.
Methods: mtDNAcn was measured in 90 antipsychotic-naïve / free schizophrenia (SCZ) patients and 147 Healthy Controls (HC). The relative mtDNAcn was determined by quantitative real-time polymerase chain reaction (qPCR) using TaqMan® multiplex assay method.
Results: Independent sample t-test revealed a statistically significant difference between groups [$t = 5.22$, $P < 0.001$] with significantly lower mtDNA copy number in SCZ compared to HC. Since age and sex can affect mtDNAcn, ANCOVA was performed with same variables, along with age and sex as covariates. The group differences persisted even after controlling for age and sex [$F(4, 232) = 22.68$, $P < 0.001$, $\eta 2 = 0.09$].
Conclusions: The study results report a significant reduction in mtDNAcn in schizophrenia patients, suggesting mitochondrial dysfunction. Lower mtDNAcn in SCZ compared to HC suggests that mtDNAcn may hold potential to serve as an important proxy marker of mitochondrial function in antipsychotic-naïve/free SCZ patients.
Supported By: CEIB Programme Support Grant to GV (BT/PR5322/COE/34/8/2012) as well as by the Wellcome Trust / DBT India Alliance Senior Fellowship research grant to GV (500236/Z/11/Z). VS is supported by the Indian Council of Medical Research (DHR/HRD/Young Scientist/Type-VI-(2)/2015)
Keywords: Schizophrenia, Antipsychotic-naïve, Mitochondrial Dysfunction, Mitochondrial DNA, Oxidative Stress

T200. miRNA-19 as a Key Player in the Modulation of the Immune System and Neuroplasticity During Neurodevelopment: Impact on the Risk for Psychosis

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Background: Early life stressful events are often associated with an increased risk of developing psychiatric disorders, such as psychosis, later in life. However, not all the stress-exposed individuals suffer from such illnesses as they develop coping or resilience strategies. The molecular mechanisms underlying the vulnerability or resilience to stress remain unclear, but epigenetics, such as microRNAs (miRNAs), may be involved.
Methods: We focused our attention on miR-19, which is involved in neurodevelopment and in schizophrenia (SZ). We measured by Real Time PCR the miR-19 expression levels in different tissues and models, such as: i) brain samples of prenatal stressed (PNS) and chronic mild stressed (CMS) rats, ii) human hippocampal progenitor stem (HPS) cells treated with cortisol and iii) blood samples from controls characterized for childhood trauma and from SZ patients.
Results: We found a significant downregulation of miR-19 in proliferating HPCs treated with cortisol as well as in the hippocampus of adult rats exposed to PNS. Similarly, CMS caused a downregulation in the miR-19 levels, but only in vulnerable rats. Alterations in miR-19 levels were observed also in blood of controls with a childhood trauma history and in SZ patients, as compared to controls.
Conclusions: MiR-19 is a target of stress and can influence the vulnerability of developing stress related psychiatric illnesses. MiR-19 can be considered a biomarker of stress vulnerability and, thus, useful in identifying subjects at high risk for psychosis. Moreover, therapies targeting miR-19 may be useful in preventing such stress related vulnerability.
Supported By: ERANET NEURON
Keywords: microRNA, Neurodevelopment, Psychosis Risk, Stress, Childhood Trauma

T201. Altered Parvalbumin-Expressing Basket Cell Terminals in the Cortical Visuospatial Working Memory Network in Schizophrenia

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Background: Impairments in cognitive domains, such as visuospatial working memory, are core features of schizophrenia. Visuospatial working memory depends on 1) information processing across primary visual (V1), posterior parietal (PPC) and dorsolateral prefrontal (DLPFC) cortices, and 2) within these regions, on the synchronous activity of neural circuits composed of excitatory pyramidal neurons and inhibitory, GABA-releasing, parvalbumin-expressing basket cells (PVBCs). In schizophrenia, protein levels of the GABA synthesizing enzyme, GAD67, are lower in the axon terminals of layer 3 PVBCs in the DLPFC. To determine if these alterations are conserved across regions of the visuospatial working memory network, we quantified GAD67 levels in PVBC axon terminals in layer 3 of V1, PPC and DLPFC from 20 matched pairs of schizophrenia and comparison subjects.
Methods: Immunofluorescence microscopy was used to quantify GAD67 protein levels in PVBC axon terminals, identified as puncta quadruple-labeled for parvalbumin, GAD67, vesicular GABA transporter, and the 65 kDa isoform of glutamic acid decarboxylase.
Results: Preliminary analyses suggest that in comparison subjects, GAD67 protein levels in PVBC terminals are highest in V1 (1345 arbitrary units [a. u.]), intermediate in PPC (1161 a. u.), and lowest in PFC (1068 a. u.). In schizophrenia, GAD67 protein levels in these terminals were 28% lower in V1, 33% lower in PPC, and 19% lower in DLPFC compared to comparison subjects.
Conclusions: PVBC alterations are conserved across regions of the V1-PPC-DLPFC network, supporting the hypothesis that common pathological mechanisms might give rise to similar neural circuit alterations across the network in schizophrenia.
Supported By: MH103204, NIH
Keywords: Fluorescence Microscopy, Glutamic Acid Decarboxylase 67, Parvalbumin Interneurons, Visuospatial Working Memory

T202. Expression of Stau2-Regulated Transcripts Across the Cortical Visuospatial Working Memory Network in Schizophrenia

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Background: Working memory, which depends on the coordinated activity of a distributed cortical network, is impaired in schizophrenia. Within one node of this network, the dorsolateral prefrontal cortex (DLPFC), levels of regulator of G protein signaling 4 (RGS4), which regulates intracellular signaling via G proteins, have been consistently shown to be lower in schizophrenia. Recent studies suggest that the RNA-binding protein, staufen2 (stau2) is an upstream regulator of RGS4 and of certain actin-regulating mRNAs that also show altered expression in schizophrenia. Here, we quantified the expression of these transcripts across four cortical areas in the visuospatial working memory network.
Methods: Transcript levels of RGS4, stau2 and 6 actin-regulating genes were quantified in the total gray matter of DLPFC, posterior parietal cortex, and primary and secondary visual

cortices from 20 matched pairs of schizophrenia and comparison subjects using qPCR.
Results: In comparison subjects, transcript levels of RGS4, CDC42EP4, RhoA and septin9 decreased, whereas transcript levels of stau1, stau2, LIMK1 and CDC42EP2 increased, from rostral-to-caudal cortical areas. In schizophrenia subjects, transcript levels of RGS4 were lower in all regions, whereas transcript levels of stau1, CDC42EP2, CDC42EP4, RhoA and septin9 were higher with significant diagnosis-area interactions across the four cortical areas. Transcript levels of stau2 and LIMK1 did not differ between the groups and only LIMK1 had a significant diagnosis-area interaction.
Conclusions: These results suggest that altered expression patterns of RGS4 and actin-regulating transcripts across the visuospatial working memory might contribute to the molecular substrate for working memory impairment in schizophrenia.
Supported By: NIMH: P50 MH103204; JSPS: 17K16394; SENSHIN Medical Research Foundation
Keywords: Postmortem Human Brain, Schizophrenia, Working Memory, RNA-binding Proteins, Actin Cytoskeleton

T203. Methylation and Transcription of BAIAP2 and DLG1, Regulators of Dendritic Spine Structure and Function, in the Postmortem Brain of Schizophrenia Subjects

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Background: Dendritic spine density (DSD) is reduced in the cortex of postmortem brains from schizophrenia (SZ) subjects. The molecular mechanisms underlying this intermediate phenotype is poorly understood. DNA methylation (DNAm), the addition of a methyl group to a cytosine nucleotide, regulates gene transcription and may be a contributing molecular mechanism.
Methods: We tested the hypothesis that DNAm correlates with DSD in the human postmortem superior temporal gyrus (STG) and that this relationship is disrupted in SZ. We measured genome-wide DNAm in the STG from 48 pairs of SZ-control subjects in which DSD had previously been identified. We used targeted bisulfite sequencing and quantitative PCR to further characterize DNAm-DSD correlations and investigate DNAm-gene transcription relationships for candidate genes.
Results: We identified an enrichment of DNAm-DSD correlations in control, but not SZ, subjects. From these data, we nominated 2 candidate genes for mediating DSD abnormalities in SZ: brain-specific angiogenesis inhibitor 1-associated protein 2 (BAIAP2) and discs large, drosophila, homolog of, 1 (DLG1). Upon further characterization of our candidate genes, we found DNAm at multiple sites throughout the BAIAP2 and DLG1 regions of interest to correlate with DSD. Further, we found expression of BAIAP2 transcripts is increased, and DLG1 transcript expression is decreased, in the STG of SZ subjects.
Conclusions: Together, these data suggest that altered DNAm in SZ may be a mechanism for SZ-related DSD reductions and identify BAIAP2 and DLG1 as promising candidate genes through which this mechanism may act.
Supported By: NIH Grants RO1 MH071533 (RAS), RO3 MH108849 (YD), KL2 TR001856 (BCM), and K23 MH112798 (BCM).
Keywords: DNA Methylation, Epigenetics, Schizophrenia, Dendritic Spines, Human Postmortem Brain

T204. Treatment of Negative Symptoms of Schizophrenia With tDCS (Transcranial Direct Current Stimulation): A Randomized, Sham-Controlled, Double-Blinded Clinical Trial

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Background: The negative symptoms of schizophrenia cause significant distress and impairment. The treatment of them is a challenge, with medications having little effect. New treatments are necessary for this condition. The aim of the study was to ascertain the efficacy of tDCS in treating negative symptoms.
Methods: This study is a randomized, sham-controlled, double-blinded trial using tDCS for the treatment of negative symptoms of schizophrenia. 100 (here we analyzed only 70% of the sample, the remaining will be presented at the meeting) patients will be enrolled and submitted to ten tDCS session over the left dorsolateral prefrontal cortex (anodal stimulation) and left temporo-parietal junction-left (cathodal stimulation), over 5 consecutive days. The primary outcome was change in the scores of the Negative Subscale of Positive and Negative Symptoms Syndrome (PANSS). Our secondary outcomes consist of others scales as SANSS (Scale of Assessment of Negative Symptoms), Calgary and the AHRS (Auditory Hallucinations Rating Scale).
Results: From 70% of the sample the active tDCS was significantly superior to sham at endpoint at 6 weeks by negative sub scale of PANSS (mean difference, 3,5 points; SD=6.2; $P<.05$). The total PANSS and the hallucinations scale had no differences between both groups.
Conclusions: The results of our studies suggest a potential role of tDCS for the treatment of negative symptoms of schizophrenia. The effect size was small. This is the biggest study with tDCS for treating negative symptoms of schizophrenia until now. At the meeting all the data will be analyzed (100 patients), it these could change our preliminary results.
Supported By: SMRI
Keywords: Transcranial Direct Current Stimulation (tDCS), Schizophrenia, Schizoaffective Disorder, Clinical Trials

T205. Effect of BI 409306 on Positive and Negative Syndrome Scale in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Phase II Trial

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Background: BI 409306, a potent, selective phosphodiesterase-9-inhibitor, was administered to patients with chronic schizophrenia; effects on cognition were studied.
Methods: This 12-week Phase II, multicenter, double-blind, placebo-controlled, parallel-group study, randomized (2:1:1:1:1) patients (18−55 years) with schizophrenia to once-daily placebo or BI 409306 (10, 25, 50, or 100 mg). Primary endpoint has been reported. Prespecified safety analyses included disease worsening (assessed by Positive and Negative Syndrome Scale [PANSS]). Post hoc analysis of PANSS: BI 409306 vs placebo-associated worsening (any, >5%, >10%, >15%, >20% increase) from baseline.
Results: Prespecified analyses (BI 409306, n=343; placebo, n=173): no meaningful change in PANSS scores; no difference between treatment groups. Post hoc analysis: more patients taking placebo, vs BI 409306, had significant worsening of PANSS positive subscale (any, 34.4% vs 27.9%; >5%, 33.8% vs 27.3%; >10%, 21.7% vs 14.1%; >15%, 15.3% vs 7.5%; >20%, 7.6% vs 4.1%), total (placebo vs BI 409306: any, 34.4% vs 31.4%; >5%, 19.8% vs 17.2%; >10%, 10.2% vs 10.0%; >15%, 7.6% vs 5.0%; >20%, 5.1% vs 3.5%) and psychopathology (placebo vs BI 409306: any, 35.7% vs 31.7%; >5%, 26.1% vs 23.2%; >10%, 15.9% vs 14.4%; >15%, 10.2% vs 8.2%; >20%, 7.0% vs 3.1%) scores, but not negative subscale (placebo vs BI 409306: any, 32.5% vs 35.4%; >5%, 32.5% vs 31.0%; >10%, 18.5% vs 18.5%; >15%, 10.2% vs 12.9%; >20%, 5.7% vs 8.2%) scores.
Conclusions: BI 409306 was advantageous over placebo for changes in PANSS positive, total, and psychopathology scores, but not for the negative subscale.
Supported By: Boehringer Ingelheim (1289.6/NCT02281773)
Keywords: Schizophrenia, PDE-9 Inhibitor, Cognition, Clinical Trials

T206. Is Mirror Neuron System Plastic in Schizophrenia? A Single Blind Randomized Controlled Trial of Add-On Yoga Therapy

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Background: A hypo-active mirror neuron system (MNS) has been associated with negative symptoms and social cognition deficits in Schizophrenia. Yoga therapy is an Indian traditional multicomponent practice, includes physical postures, breath regulation, and mindfulness techniques. Through therapist-guided imitation of body postures, Yoga is hypothesized to modulate the dysconnection in MNS and resulting in better social-connectedness. Exploring effects on MNS may provide a biologically plausible framework for understanding therapeutic benefits of yoga.
Methods: 30 consenting subjects with diagnosis of Schizophrenia were stabilized on anti-psychotics and randomized to either yoga therapy group (YTG) (N =17) or Treatment as usual (TAU) (N=13) Transcranial magnetic stimulation (TMS) used as a non-invasive method to measure Mirror neuron activity(MNA) during static image and action-observation paradigms. The data was analyzed using Repeated measures ANOVA and pearson's correlation.
Results: The baseline clinical characteristics and TMS stimulation parameters of both YTG and TAU groups were not different statistically. MNA measured using short interval intracortical inhibition(SICI) showed significant difference in YTG(n=17) when compared to TAU group(n=13) [F(df) 1.890(1) p=0.056] There is a positive correlation between SICI and Social cognition composite score [pearson's coefficient r(0.543) p=0.002]
Conclusions: Learning and performing coordinated physical postures with a teacher facilitates imitation which could reinforce the premotor and parietal mirror neuron system as noted in statistically significant improvement in MNA measured using SICI in YTG compared to TAU group, suggestive of improvement in GABA-A neurotransmission. MNS could be a potential mediator in causing improvement in social cognition. This study substantiates the benefit of add-on yoga therapy among patients of schizophrenia.
Keywords: Schizophrenia, Social Cognition, Mirror Neurons System, Yoga Therapy, Randomized Controlled Trial

T207. Schizophrenia Patients in Community-Based Residential Care are Able to Benefit From Auditory-Based Targeted Cognitive Training: Improvement in Cognitive Measures and Positive Symptoms

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Background: Impairments in information-processing contribute to higher-order cognitive deficits in schizophrenia (SZ). No currently approved treatment strategies target these disease processes, but recently targeted cognitive training (TCT) has been shown to be effective in attenuating neurocognitive impairment in SZ. Despite encouraging results, previous studies have been largely conducted in academic settings using relatively young SZ outpatients. Whether TCT is effective in more disabled, older SZ patients remains to be seen. We report preliminary findings from an ongoing randomized clinical trial investigating the effectiveness of TCT in SZ patients in a community-based residential care facility specializing in long-term rehabilitation.

Methods: SZ patients were randomized to treatment as usual (TAU; n=24) or treatment as usual + TCT (n=22). Average duration of illness was approximately 15 years. Auditory discriminability (Word-In-Noise test, WIN), cognitive functioning (MATRICS Consensus Cognitive Battery, MCCB), as well as positive (SAPS) and negative symptoms scores (SANS) were assessed before and after TCT. Data were analyzed using linear mixed effects models.
Results: At follow up, TCT was associated with significant improvements in WIN (d=0.63, $p<0.04$), verbal learning and memory (d=0.82 $p<0.01$), and SAPS (d=-0.62, $p<0.05$). Age was a significant moderator of verbal learning gains with TCT; older patients exhibited greater improvements ($p<0.01$).
Conclusions: TCT significantly improved auditory discrimination, verbal learning and positive symptoms in SZ patients in community-based residential care. Our results suggest older SZ patients may be able to benefit from TCT. Improving the fidelity of low-level auditory sensory information processing via TCT may yield clinically meaningful outcomes, even in patients with chronic illness.
Supported By: This work was supported by the Sidney R. Baer, Jr. Foundation, the Brain and Behavioral Research Foundation, VISN-22 Mental Illness Research Education and Clinical Center (MIRECC), and National Institute of Mental Health of the National Institutes of Health (K23 MH102420).
Keywords: Schizophrenia, Schizoaffective Disorder, Cognitive Remediation, Clinical Trials

T208. Transplantation of Isolated Mitochondria Restores Schizophrenia-Related Deficits In-Vitro and In-Vivo

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Background: Malfunction of mitochondria is repeatedly demonstrated in schizophrenia (SZ). Recent studies have reported improvement of cellular and mitochondrial functions following mitochondrial transplantation. Here we aimed to study the effect of transplantation of isolated active normal mitochondria (IAN-MIT) on SZ-related deficits in-vitro and in-vivo.
Methods: We studied mitochondrial cell entrance and function, neuronal differentiation and behavioral responses in the latent inhibition test, using two experimental models: SZ-derived lymphoblasts and induced pluripotent stem cells (iPSCs) differentiated into glutamatergic neurons, and the poly-I:C rat model of SZ.
Results: IAN-MIT entrance and short-term survival were observed by the presence of JC1-stained IAN-MIT and of their mtDNA haplotype in host cells for at least 3 days. Long-term effects were demonstrated by the improvement of mitochondrial respiration, membrane potential ($\Delta\psi m$) and network dynamics in SZ-derived lymphoblasts. Transplantation of IAN-MIT into differentiated SZ-iPSCs improved their impaired mitochondrial activity, differentiation into glutamatergic neurons and synaptic connectivity. In rats, a long-lasting beneficial effect was demonstrated in adulthood following a bilateral injection of IAN-MIT into the medial-prefrontal cortex in adolescence. In the adult poly-I:C model rats, IAN-MIT transplantation prevented disrupted latent inhibition and restored $\Delta\psi m$ to normal levels in isolated neurons from their frontal cortex. However, in controls, IAN-MIT induced a detrimental effect on both phenomena.
Conclusions: Our findings suggest a direct link between mitochondrial function and SZ-related deficits in-vitro and in-vivo. Moreover, IAN-MIT transplantation provides evidence for a relationship between mitochondria and behavior, being beneficial when mitochondrial function is impaired while interfering with the homeostasis of mitochondrial diverse functions under normal conditions.
Supported By: The Israel Science Foundation (ISF); The National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD); The Rambam Medical Center - Ophakim.
Keywords: Mitochondrial Dysfunction, Schizophrenia, Prenatal poly-I:C Rat Model, Isolated Active Normal Mitochondria Transplantation, hiPSCs-Derived Neurons

T209. Selective DISC1 Knockdown in Astrocytes Produces Region-Dependent Effects on Cognitive Function

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Background: Disrupted-In-Schziophrenia-1 (DISC1) is a gene, rare highly penetrant mutations in which have been associated with major psychiatric disorders. While we have a good understanding of the roles of DISC1 in neurons, the possible functions of DISC1 in astrocytes remain largely unknown. We studied region-dependent molecular, cellular, and behavioral effects of astrocyte-selective knockdown of Disc1 in mice
Methods: 2-month-old C57BL/6 male mice received single bilateral injections of either AAV1-GFAP::GFP-miR30-Disc1 (Disc1 KD) or AAV1-GFAP::GFP-miR30-Scrambled (Control) into the CA1-2 areas of the hippocampus or the prelimbic area of the frontal cortex. Two weeks later, mice were tested in a series of behavioral tests, including social interaction, Barnes maze, and trace fear conditioning. Upon completion of behavioral testing, we assessed gene expression or cell morphology in GFP-labeled Disc1 KD and control astrocytes
Results: Disc1 KD in the hippocampus decreased sociability, social novelty preference, and impaired performance in the Barnes maze and trace fear conditioning. In contrast, Disc1 KD in the frontal cortex decreased performance in the Barnes maze without affecting trace fear conditioning. We observed no effects of Disc1 KD on locomotor activity or anxiety after either regional injection. We also found region-dependent alterations in astrocyte morphology and expression of astrocyte-specific factors following Disc1 KD
Conclusions: Our results indicate that DISC1 in astrocytes may be involved in maintenance of cell morphology and support of neuronal activity required for cognitive function.

Different cortical and hippocampal effects of Disc1 KD are consistent with a growing appreciation of regional heterogeneity in astrocyte pathophysiology relevant to cognitive disorders

Supported By: 4 R01 MH083728-07

Keywords: Cognitive Function, Astrocytes, DISC1, Prefrontal Cortex, Hippocampus

T210. Influence of Early Visual Encoding on Working Memory Performance and its Dysfunctions in Schizophrenia

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Background: Working Memory (WM) deficits are a cardinal feature of schizophrenia proposed to underlie many of the patient's day-to-day difficulties. We have previously demonstrated a relationship between neural measures of visual stimulus encoding and WM performance in schizophrenia using EEG. However, the mechanism underlying this relationship is poorly understood. Here we investigated whether WM encoding of stimuli defined by purely luminance or chromatic information would differentially influence WM performance and early visual ERP responses in typical populations and in patients with schizophrenia.
Methods: Patients with schizophrenia and matched typical participants performed a modified delayed discrimination WM task while we recorded a 64 channel EEG. Stimuli for the WM task were defined along different directions in cardinal colour space (Derrington et al, 1984) to create stimuli that were isolating the luminance or two different chromatic mechanisms.
Results: Results showed that luminance-defined shapes resulted in higher WM accuracy and faster reaction times. Early visual ERPs (P1 and N2) responded preferentially to luminance and chromatic stimuli, respectively. This was not the case in patients as both the performance and ERPs were reduced.
Conclusions: Our results confirm the link between deficits in the early encoding phase and WM performance. These impairments may have an impact on everyday life of people with Schizophrenia.
Supported By: NARSAD
Keywords: Schizophrenia, Working Memory, ERPs, Visual Processing

T211. Emotional Context Restores Cortical Prediction Error Responses in Schizophrenia

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Background: The mismatch negativity (MMN) deficit in schizophrenia is a consistently replicated finding and is considered a potential biomarker. From the cognitive neuroscience perspective, MMN represents a cortical correlate of the prediction error, a fundamental computational operator that may be at the core of various cognitive and clinical deficits observed in schizophrenia. The impact of emotion on cognitive processes in schizophrenia is insufficiently understood, and its impact on basic operators of cortical computation is largely unknown.
Methods: In the visual domain, the facial expression mismatch negativity (EMMN) offers an opportunity to investigate basic computational operators in purely cognitive and in emotional contexts. In this study, we asked whether emotional context enhances cortical prediction error responses in patients with schizophrenia, as is the case in normal subjects. Therefore, seventeen patients with schizophrenia and eighteen controls completed a visual sequence oddball task, which allows for directly comparing MMN components evoked by deviants with high, intermediate and low emotional engagement.
Results: Interestingly, patients with schizophrenia showed pronounced deficits in response to neutral stimuli, but almost normal responses to emotional stimuli. The dissociation between impaired MMN and normal EMMN suggests that emotional context not only enhances, but restores cortical prediction error responses in patients with schizophrenia to near-normal levels.
Conclusions: Our results show that emotional processing in schizophrenia is not necessarily defect; more likely, emotional processing heterogeneously impacts on cognition in schizophrenia. In fact, this study suggests that emotional context may even compensate for cognitive deficits in schizophrenia that are, in a different sensory domain, discussed as biomarkers.
Keywords: EEG, MMN, Emotion, Faces, Schizophrenia

T212. Does Manipulating Visual Scanpaths During Facial Emotion Perception Modulate Brain Activation in Face-Processing Regions in Schizophrenia Patients and Controls?

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Background: Recent studies suggest that functional activation during face perception is modulated by the viewer's gaze behaviour. These findings are of particular relevance for schizophrenia, a disorder characterized by impaired facial emotion recognition, activation abnormalities in the neural system for face perception, and reduced fixations to salient facial features compared to controls. We examined the relationship between gaze behaviour and brain activation during facial emotion perception in schizophrenia.
Methods: 23 schizophrenia patients and 26 controls underwent fMRI while viewing pictures of emotional faces. During

the Typical Viewing condition, a fixation cue directed participants' gaze primarily to the eyes and mouth, while gaze was directed to peripheral features during the Atypical Viewing condition. fMRI BOLD data were analyzed using whole-brain and a-priori ROI analyses.
Results: Both conditions elicited activation throughout the facial emotion perception network. Typical Viewing led to greater activation in extrastriate cortex, while Atypical Viewing elicited greater activation in primary visual cortex and regions involved in oculomotor control ($Z>3.1$, $p<0.05$, FWE-corrected). ROI analyses confirmed that greater activation during Typical than Atypical Viewing extended to the 'occipital face area' (OFA) ($p<0.05$, FWE-corrected). No significant interactions between viewing condition and group were observed.
Conclusions: Directing gaze toward salient facial features leads to increased activation in visual association cortex including the OFA, but not in other regions of the facial emotion perception network. These results indicate that gaze behaviour modulates activation in early face-processing regions, suggesting that abnormal gaze behaviour in schizophrenia may contribute to the documented activation abnormalities in these regions during facial emotion perception.
Supported By: Alberta Innovates; Canadian Institutes of Health Research; University of Calgary
Keywords: Schizophrenia, Face Perception, Facial Emotion, fMRI

T213. Meg Resting State Oscillations and Their Relationship to Clinical Symptoms in Schizophrenia

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Background: Neuroimaging studies suggest that schizophrenia is characterized by disturbances in oscillatory activity, although at present it remains unclear whether these neural abnormalities are driven by dimensions of symptomatology. In the present study we examined whether neural oscillations in the delta, theta, alpha, beta and gamma bands correlate with positive symptoms and negative symptoms in schizophrenics (SZ) during rest.
Methods: Resting-state brain activity of 39 SZ and 25 controls was recorded using magnetoencephalography. SZ were categorized based on the severity of their positive symptoms – low (LP) vs. high (HP), and negative symptoms – low (LN) vs. high (HN).
Results: Power spectrum analysis revealed that HP showed lower alpha power than controls in numerous areas within the brain, and alpha power was negatively correlated with positive symptoms. In contrast, HN showed greater beta power than LN, and controls in trend, and beta power was positively correlated with negative symptoms. The alpha band effect encompassed the whole brain, whereas the beta band effect was present in the left hemisphere only.
Conclusions: In light of the alpha band sensory gating framework and beta band cognitive status quo framework, these findings might suggest that SZ with HP are characterized by a cognitive or sensory overload, marked by reduced alpha power, and that SZ with HN are characterized by a cognitive inflexibility, marked by enhanced beta power. These findings suggest that alpha and beta power are potential biomarkers for distinguishing between controls and SZ with HP and between SZ with HN and those with LN, respectively.
Supported By: The work was supported by the German-Israeli Foundation for scientific research and development (grant 1071)
Keywords: Schizophrenia, MEG, Resting State, Positive Symptoms, Negative Symptoms

T214. Two Sisters Too Many: A Case of Benzodiazepine Withdrawal-Induced Reduplicative Paramnesia

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Background: Hallucinations have been reported with long-term use of benzodiazepines (Ashton, 1984) with a small number of cases following withdrawal from benzodiazepines (Roberts, 1986). Reduplicative paramnesia is a subset of delusional misidentification syndrome (Politis, 2012) characterized by a belief of duplication in a familiar person, place, or object (Blom, 2010). Reduplicative paramnesia has not been reported resulting from benzodiazepines withdrawal.
Methods: Case Report: The patient, a 39-year-old right-handed male three days following abrupt discontinuation of 4 mg per day of alprazolam, hallucinated two copies of his sister. At the same time, the patient would hear a mechanical male voice with command hallucinations to eliminate the imposters leading the patient to charge towards the sisters with a knife in an attempt to kill them. The reduplicative hallucination remained until the patient consumed 2 mg of alprazolam and fell into sleep for approximately six hours.
Results: Abnormalities in Neurological Examination: Cranial nerves IX and X: uvula deviated to the left. Motor: drift test with right abductor digiti minimi sign. Cerebellar: finger-to-nose dysmetria bilaterally. Low amplitude, high frequency tremor on extension on both upper extremities. Reflexes: 0 branchioradialis, 1+ biceps, 0 triceps, 0 quadriceps femoris, 1+ right ankle jerk, and 0 left ankle jerk.
Conclusions: Reduplicative paramnensia is typically associated with lesions in the right frontal lobe (Kapur, 1988). However, reduplicative paramnesia cannot be assumed to exist merely in the context of frontal lobe lesions. In patients presenting with such poly-optic hallucinations, query as to benzodiazepine withdrawal is warranted.
Supported By: Smell and Taste Treatment and Research Foundation
Keywords: Benzodiazepine Withdrawal, Reduplicative Paramnesia, Hallucinations, Alprazolam

T215. EEG Spectral Analysis of Social Aversive Conditioning in Psychosis and Clinical Risk

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Background: Socio-emotional impairments are common in schizophrenia and are linked to poor prognosis. Physiological studies of emotion processing can increase our understanding of the nature and course of these deficits. We used aversive conditioning of social stimuli to probe learning and responsivity to emotional valence in both clinical risk youth and patients. EEG spectral analysis assessed differential processing of aversively conditioned stimuli during anticipation of the aversive outcome.
Methods: Young people (ages 10-30) at clinical risk for psychosis (CR, n=51), with psychosis (PS, n=28) or otherwise healthy (HC, n=35) completed a delayed aversive conditioning task under EEG recording. Three neutral faces were followed by an aversive tone on 100%, 50% or 0% of trials. Alpha (8-12Hz) and gamma (30-50Hz) power, reflecting arousal and integration respectively, were examined across dimensions of aversiveness (100% vs 0%) and unpredictability (50% vs 100%+0%).
Results: Behaviorally, all groups learned the associations between faces and outcomes. CR failed to show the normal arousal response (reduced alpha power) following faces signaling aversive or uncertain outcomes. PS exhibited reduced gamma power when anticipating an aversive outcome, but increased gamma when the outcome was uncertain. Abnormalities correlated with negative symptoms.
Conclusions: Emotion processing abnormalities may be physiologically distinct in subclinical vs. frank psychosis. Poor neural integration of emotionally salient stimuli, as indexed by gamma, may contribute to negative symptoms of schizophrenia. For CR, the deficit in arousal response may reflect an inability to regulate responses to negative social cues, which is distinct from both healthy and overt disease states.
Supported By: National Institute of Mental Health Conte Center P50MH096891; RC2MH089983, RC2MH089924, T32 MH019112, R01MH-107235, and R01MH101111; Lifespan Brain Institute (LiBI) of Penn Medicine and the Children's Hospital of Philadelphia
Keywords: Clinical High Risk for Psychosis, EEG, Fear Conditioning, Social Cognition, Emotional Reactivity

T216. Deficient Belief Updating Explains Abnormal Information Seeking Associated With Delusions in Schizophrenia

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Background: Delusions are false beliefs held with high conviction despite contradictory evidence. While Bayesian inference has long been proposed to underlie delusions, previous attempts to show this have not yielded compelling evidence. Here, using a modified, incentive-compatible information-sampling task, we sought a mechanistic understanding of delusional severity among a sample of 26 medicated and unmedicated patients with schizophrenia and 25 matched healthy controls.
Methods: On each trial, participants decided whether to draw beads from one of two hidden jars - the identity of which was determined by their majority bead color, blue or green - or to guess the identity of the hidden jar, in order to minimize financial losses. Before each choice between drawing and guessing, participants gave a probabilistic estimate reflecting their confidence about the identity of the hidden jar.
Results: In contrast with previous work using hypothetical decision-making, increased information seeking (i.e., increased draws-to-decision) specifically correlated with delusional severity in patients (r=0.51, p=0.01). Draw-wise probability estimates of the identity of the hidden jar further indicated that high-delusion patients had abnormal belief updating characterized by increased reliance on prior evidence, which further correlated with increased information seeking (r=0.46, p=0.023).
Conclusions: These results thus suggest that abnormal belief updating, characterized by excessive reliance on prior information, may be a core computational feature underlying delusional belief formation or maintenance in psychosis. This computational mechanism may be a higher-level counterpart of increased reliance on prior information in hallucination-prone individuals during lower-level sensory discrimination, thus suggesting a convergent mechanism that may potentially explain psychosis more broadly.
Supported By: NIMH K23-MH101637
Keywords: Delusions, Bayesian Model, Computational Psychiatry, Schizophrenia, Causal Inference

T217. Measures of Neural Oscillation Synchrony During Reward Processing in Schizophrenia

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Background: Relatively little is known about the extent to which reward processing deficits persist in schizophrenia in the absence of response planning and execution demands. We therefore used a passive reward paradigm to assess neural oscillation synchrony during anticipation and receipt of monetary rewards in patients with schizophrenia (n=45) in comparison to demographically-matched healthy controls (n=42).
Methods: EEG was recorded while participants completed 288 trials of a slot machine task. Wins occurred when 3 identical fruit symbols were populated in the slot reels (P=.25); Near Misses occurred when the first and second reel symbols were identical but the third reel symbol was incongruent (P=.25). Total Misses occurred when the first two reels were incongruent (P=.50). In addition to winning outcomes, we focused on brain responses to near misses, losing trials that

are perceptually close to a win and associated with increased motivation to play. Event-related power and phase-locking (inter-trial coherence) time-locked to reward evaluation were extracted within canonical frequency bands and assessed for task condition and group differences.
Results: There was a significant Group-by-Condition interaction ($p = .02$) within the alpha power band, observed across distributed, bilateral posterior electrode sites. This effect was explained by greater alpha desynchronization elicited by winning, relative to nearly missing, that was observed in healthy controls and significantly attenuated in patients with schizophrenia.
Conclusions: These findings implicate altered alpha power during outcome evaluation of rewarding events in schizophrenia, even when reward attainment places minimal demands on higher-order cognitive processes.
Supported By: VA
Keywords: Reward Processing, Electroencephalography (EEG), Neural Oscillations, First Episode Schizophrenia

T218. Reduced Amplitude of Fixation-Related Potentials Predicts Impaired Serial Search Performance in Schizophrenia

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Background: Visual evoked potentials are traditionally obtained in response to external stimuli (flash, gratings) and have been shown to be abnormal in schizophrenia patients (SCZ), supporting theories of early visual dysfunction. However, there is increasing realization that visual ERP are also elicited by fixations, giving rise to fixation evoked ("lambda") responses that are morphologically similar to the visual P1. Here we utilized a combined eye-tracking and neurophysiological approach during serial visual search to investigate the underlying neural dysfunction in SCZ.
Methods: EEG and eye movements were recorded continuously with standard methods from 25 healthy controls (HC) and 24 SCZ performing a visual search task. Subjects searched for a low contrast horizontally oriented Gabor patch within 47 evenly-distributed distractors that matched either direction or contrast of the target. EEG epochs were averaged to the onset of fixations, with triggers obtained from the eye tracker.
Results: SCZ had more fixations per trial ($p = .008$) and longer trial lengths ($p = .009$) than HC.

Fixation-related P1 had similar scalp distributions in both groups but reduced amplitude in patients ($p=.009$). Analysis of fixations on targets vs non-targets showed higher P1 to fixation on the target ($p<.000$), with no interaction. P1 amplitude to targets correlated with the number of fixations ($p=.015$) and mean trial time ($p=.021$), but not with fixation duration.
Conclusions: SCZ patients show impaired performance on serial visual search that is related to decreased amplitude of the fixation-related P1. These results support the use of fixation ERP to probe early stages of visual processing in SCZ.
Supported By: The study was supported by a NIMH grant (MH049334) awarded to Daniel Javitt, M.D., Ph.D.
Keywords: Schizophrenia, Electroencephalography (EEG), Visual Processing, Eye Tracking

T219. Effects of Tolcapone on Sensorimotor Gating in Healthy Adults

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Background: Sensorimotor gating of startle measured by prepulse inhibition (PPI) is regulated by prefrontal cortex (PFC) and ventral striatal dopamine. Tolcapone, a reversible catechol-O-methyl transferase (COMT) inhibitor, increases PFC dopamine tone. Previous studies in Greek conscripts reported that tolcapone increased PPI in men homozygous for the valine allele at the COMT polymorphism, rs4680. We previously reported pro-cognitive effects of tolcapone in healthy adults; here we report the effects of tolcapone on PPI in these subjects.
Methods: Tolcapone effects on PPI were analyzed in rs4680-genotyped adults ($n=17$) using a double-blind, within-subject design; stimulus parameters were identical to those previously reported to be tolcapone-sensitive. PPI was analyzed by ANOVA, using dose (placebo vs. 200 mg) and prepulse parameters (intensity, interval) as within-, and sex and rs4680 genotype as between-subject factors.
Results: No significant tolcapone effects were detected on startle magnitude, habituation or latency. ANOVA of PPI revealed expected main effects of prepulse intensity and interval ($p's<0.0001$), and significant interactions of dose x intensity x interval ($p<0.025$) and dose x intensity x interval x genotype ($p=0.05$). Post-hoc analyses revealed PPI-enhancing effects of tolcapone with 75 dB(A) prepulses at 120 ms prepulse intervals ($p<0.03$); increased PPI reflected tolcapone effects in rs4680 Met homozygotes. Neurocognitive correlates will be reported.
Conclusions: Findings confirm the PPI-enhancing effects of tolcapone, but do not reproduce published moderating effects of rs4680. Tolcapone-enhanced PPI supports prevailing models for the PFC dopaminergic regulation of PPI. Greater tolcapone sensitivity among rs4680 Met homozygotes parallels our findings with amphetamine-enhanced PPI.
Supported By: NARSAD YI grant 2013; 1KL2TR001444; RO1MH094320
Keywords: Prepulse Inhibition, Tolcapone, COMT Val/Met, Neurocognition, Sensorimotor Gating

T220. Hippocampal Network Dysfunction and Relational Memory Deficits in Schizophrenia

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Background: Functional dysconnectivity, or the loss of coherence of functional neural networks, has long been thought to underlie cognitive impairment in schizophrenia. In particular, individual connections with the hippocampus—a consistent focal point of structural and functional changes in schizophrenia—have been associated with the marked memory deficits observed in patients. However, only recent technological advances have enabled the large-scale exploration of functional networks with accuracy and precision. Here, we use graph theory to investigate the relationship between hippocampal functional networks and memory deficits in schizophrenia.
Methods: We examined resting-state connectivity in 45 schizophrenia spectrum disorder patients and 38 healthy controls. Modularity was calculated for a core hippocampal-medial temporal lobe cortex (MTLC) network and an extended hippocampal-cortical network; follow-up analyses tested anterior and posterior divisions. Correlations were examined between modularity and relational memory ability.
Results: Hippocampal-MTLC modularity was lower in schizophrenia patients than controls ($F = 6.14$, $p = .02$), with a similar, though non-significant, pattern found in the hippocampal-cortical network ($p = .22$). Relational memory was also markedly impaired in patients ($X2 = 30.18$, $p < .0001$). Patients and controls showed a distinct brain-behavior relationship that differed by network and anterior/posterior division—while relational memory in control subjects was associated with lower anterior hippocampal-cortical modularity ($r = -.48$, $p = .004$), relational memory in schizophrenia patients trended with lower posterior hippocampal-MTLC network modularity ($r = -.32$, $p = .07$).
Conclusions: Our findings support a model of abnormal resting-state cortico-hippocampal network coherence in schizophrenia, which may contribute to relational memory deficits.
Supported By: R01 MH0805650
Keywords: Schizophrenia Spectrum, Resting State Functional Connectivity, Graph Theory, Modularity

T221. Sensorimotor Induction of Auditory Misattribution in Psychosis is Linked to Neural Disconnectivity

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Background: Schneiderian first rank symptoms (FRS) are characterized by a diminished demarcation of self-other boundaries, causing misattribution of self-generated thoughts and actions to external sources. We have shown that introducing sensorimotor prediction error (SPE) by a robotic device in healthy subjects can induce a Feeling of a Presence (FoP) which is related to the FRS (Blanke et al. 2014). Here, we tested if SPE may induce auditory misattribution in psychotic patients and if this is related to neural connectivity in the temporoparietal cortex, insular cortex and fronto-parietal cortex (FoP Network).
Methods: Participants manipulated a haptic robotic system inducing a sensorimotor conflict while performing a self-other auditory discrimination task. 31 early psychotic patients (19 with and 12 without FRS) and 20 controls participated in the experiment. We measured accuracy (d′) on auditory self-other discrimination task during sensorimotor conflict induction or control condition, functional connectivity magnitude in a priori FoP network, and calculated correlation between the two measures.
Results: Patients with FRS had reduced accuracy in auditory self-other discrimination when sensorimotor conflict was induced ($F(2, 44)=6.68$, $p=.002$). rsfMRI connectivity analysis indicated lower connectivity for these patients in regions of the FoP network compared to the non-first rank and control groups ($p=.015$, $p=.014$). The level of functional connectivity in the FoP network correlated with the reduction of self-other discrimination in the FRS+ group ($r=-0.56$, $p=.03$).
Conclusions: Experimental induction of SPE can cause self-other confusion in the auditory domain. This deficit in self-other discrimination was correlated to specifically reduced connectivity in the FoP network related to sensorimotor self-representation.
Supported By: National Center of Competence in Research (NCCR) "SYNAPSY – The Synaptic Bases of Mental Diseases" financed by the Swiss National Science Foundation (No. 51AU40_125759)
Keywords: Early Psychosis, Prediction Errors, First Rank Symptoms, Sensorimotor Processing, Robotic Stimulation

T222. Functional Brain Activation and Grey Matter Integrity in Psychosis: A Combined Functional Magnetic Resonance and Neurite Orientation Distribution and Density Imaging Study

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Background: Post-mortem studies in psychosis consistently find reduced dendritic spine density and length, which are thought to underlie deficits in neural activation and cognitive function. Using task-fMRI and neurite orientation dispersion and density imaging (NODDI), we tested the hypothesis that 1) brain activity in a distributed prefrontal-parietal network during working memory would be reduced in psychosis; 2) regions demonstrating reduced activation would also exhibit lower grey matter integrity, as measured by ODI and Vic; 3) working memory activation would correlate with grey matter integrity.

Methods: 103 psychosis participants and 53 controls completed task-fMRI and DTI scans. Group differences in activation during working memory maintenance were investigated. Regions exhibiting significant group differences were analyzed further for relationships with both cognitive performance and NODDI measures.
Results: Psychosis participants demonstrated reduced activation during working memory maintenance in bilateral superior frontal gyrus (SFG) (right: $t(154)=2.65$, $p=.009$; left: $t(154)=3.10$, $p=.002$), thalamus ($t(154)=2.87$, $p=.005$), bilateral intraparietal sulcus (IPS) (left: $t(154)=2.34$, $p=.018$; right: $t(154)=2.188$, $p=.03$), and superior parietal lobule (SPL) ($t(154)=2.155$, $p=.033$). Across all subjects, regional activation significantly correlated with task performance (right SFG: $r=.36$, $p<.001$; left SFG: $r=.23$, $p=.003$; thalamus: $r=.245$, $p=.002$; left IPS: $r=.263$, $p=.001$; right IPS: $r=.278$, $p<.001$; superior parietal cortex: $r=.44$, $p<.001$). Patients demonstrated reduced Vic in SPL ($t(154)=1.97$, $p=.05$). No other group differences were observed in ODI or Vic. BOLD activation was not significantly associated with Vic or ODI.
Conclusions: These data reveal that working memory ability and activation is abnormal in psychosis; however, these associations appear relatively independent of NODDI.
Supported By: R01-MH102266
Keywords: Working Memory, Psychotic Disorders, NODDI, Brain Imaging, fMRI, Frontoparietal Network

T223. Genetic Dissection of the Cognitive Deficits in a Novel Conditional Bacterial Artificial Chromosome Transgenic Mouse Model of Human VIPR2 Copy Number Variation (CNV)

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Background: Copy number variations (CNVs) have been convincingly shown to significantly contribute to the risk of Schizophrenia, Autism, and other childhood neuropsychiatric disorders. Intriguingly, even phenotypically healthy carriers of CNVs manifest cognitive deficits, suggesting neurodevelopmental CNVs affect cognition and may confer disease risk. Two large-scale GWAS studies pinpointed a CNV at the chromosomal locus 7q36.6 in schizophrenia patients at a rate 14 times higher than in healthy individuals, with all of the microduplications occurring within a single gene: Vasoactive intestinal peptide receptor 2 (VIPR2). VIPR2 CNV was also significantly over-represented in autism spectrum disorder
Methods: To bridge the major gap in linking candidate genetic vulnerability to dysfunctional neuronal subtypes and circuits, we have developed a conditional human VIPR2 CNV Bacterial Artificial Chromosome (BAC) transgenic mouse model that recapitulates the genetic architecture of the susceptibility allele.
Results: Using two independent transgenic founder lines with one and four human VIPR2 copies and crossing into mouse VIPR2 null background, we have confirmed functional and anatomic similarities between mouse and human VIPR2. Human VIPR2 CNV elicits dysfunctional striatal PKA signaling, accompanied by working memory deficits, social recognition deficits, and sensory gating deficits. Genetic removal of VIPR2 transgene expression selectively in striatonigral neurons rescued multiple cognitive impairments.
Conclusions: Our studies yield critical mechanistic insights on the causative pathogenic role of a neurodevelopmental CNV on cognitive circuits and behavioral manifestations. The approach of cell-type-specific targeting of cognitive deficits will shed light on novel therapeutic strategies for schizophrenia and autism patients.
Supported By: NARSAD
Keywords: CNV, Schizophrenia, Transgenic Animal Model, Genetics, Cognitive Deficits

T224. A Mouse Model of the 3q29 Deletion

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Background: 3q29-deletion syndrome is associated with decreased birth weight and a delayed growth trajectory, as well as intellectual disability, anxiety, autism, and >40-fold increased risk for schizophrenia. To test the hypothesis that haploinsufficiency of the DLG1 gene within the interval is driving these phenotypes, we generated 3q29-deletion (Del16+/Bdh1-Tfrc) mice and compared their phenotypes to Dlg1+/-mice.
Methods: 3q29 deletion mice were generated using CRISPR/Cas9 with guide RNAs at the syntenic proximal and distal breakpoints on mouse chromosome 16. After experimental confirmation of the deletion, growth was monitored over 3 weeks starting at P8. Behavioral assays were performed in the following order: locomotor activity, elevated plus maze (EPM), Morris water maze (MWM), and prepulse inhibition (PPI).
Results: Del16+/Bdh1-Tfrc mice weighed 1-3 grams less than their wild-type littermates over the first three weeks of life consistent with the growth defects in 3q29 patients. Del16+/Bdh1-Tfrc mice displayed increased rearing (a measure of stereotypy), impaired learning and memory in the MWM, and sensorimotor gating deficits in PPI, but no anxiety-like behavior in the EPM. In contrast, we observed no abnormalities in weight or behavior with Dlg1+/- mice.
Conclusions: We have created the first animal model of the 3q29 deletion and show delayed growth and behavioral phenotypes consistent with 3q29-deletion patient phenotypes. However, Dlg1+/- mice show no weight or behavioral abnormalities. These findings suggest that the phenotypes associated with the 3q29-deletion are not solely due to haploinsufficiency of DLG1, but are instead likely a combination of genes and/or regulatory elements that contribute to the phenotypes.
Supported By: NIH R01 GM097331-01
Keywords: Schizophrenia, 3q29 Deletion, Mouse Model

T225. Burden of Rare Coding Variants in the 22q11.2 Deletion Syndrome Region is Associated With Educational Attainment and Schizophrenia Risk

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Background: The 22q11.2 deletion is associated with a strongly increased risk for schizophrenia and intellectual impairment. Here, we hypothesized that rare single nucleotide coding variants within the 22q11.2 deletion region can also exert relevant phenotypic effects.
Methods: We analyzed putative functional exonic variants in 22q11.2 (MAF<5%), obtained with the Illumina HumanExome Beadchip v1.1, to calculate their cumulative impact on 1) educational attainment in a large population sample (n= 2081), and 2) on schizophrenia risk in an independent schizophrenia case-control sample (n= 1933).
Results: To this end, we determined in each individual the number of SNVs in the minimal critical region of 22q11.2 (i.e. flanked by low copy repeats A and B). In the general population a steep decline of the proportion of individuals with high educational attainment occurred at a burden of four or more SNVs in 22q11.2 (12:2 case vs controls; p<0.05; OR=4.65). Next, we observed that the same burden, - i.e. four or more putative coding SNVs in 22q11.2 – was significantly associated with an increased risk for schizophrenia in an independent schizophrenia case-control sample (8:1 cases vs control; p< 0.05; OR=7.49).
Conclusions: We find that an increased burden of rare coding SNVs 22q11.2 is associated with lower educational attainment and an increased risk for schizophrenia. These findings have several tentative implications. First, they suggest that in a genomic region where pathogenic structural variants recurrently arise, SNVs can, cumulatively, also confer a relevant phenotypic impact. Second, they contribute to the empirical basis of the hypothesized genetic link between schizophrenia and cognitive ability.
Keywords: Genetics, Rare Variants, Schizophrenia

T226. Genotype-By-Sex Interaction Effects in the Risk for Schizophrenia, Major Depressive Disorder, and Bipolar Disorder

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Background: Sex differences in prevalence and presentation are pervasive in major depressive disorder (MDD), schizophrenia (SZ), and bipolar disorder (BD). Cross-disorder genetic risk identified by the Psychiatric Genomics Consortium (PGC) and shared sex differences in brain abnormalities suggest possible shared sex-dependent genetic risk. Thus, using PGC data, we performed genome-wide SNP-by-sex interaction analyses.
Methods: 65,536 patients (30,608 SZ, 18,958 BD, 15,970 MDD) and 93,421 controls (65%, 40%, 32%, 49% male, respectively) were included (96.7% European, 3.3% East Asian). The PGC has described sample acquisition, genotyping, quality control, and imputation. Samples were filtered for relatedness (Pi-Hat>0.1). SNPs with <0.8 imputation quality and/or <0.05 minor allele frequency were excluded. Cohort-specific logistic regression analyses were performed, with main effect and SNP-by-sex interaction terms for each SNP (additive model; ancestry covariates), followed by inverse variance-weighted meta-analyses within/across disorders.
Results: Several loci showed suggestive ($p<1x10-6$) evidence for SNP-by-sex interaction within-disorder (SZ: 3; MDD: 2; BD: 1). A chromosome-8 locus in/near IDO2 showed significant interaction in SZ (rs60545325; $p=2.8x10-9$). IDO2 encodes a protein involved in tryptophan catabolism along the kynurenine pathway, connected with inflammation, immune regulation, and neurological conditions. Another chromosome-8 locus, in ANKRD46, showed suggestive cross-disorder SNP-by-sex interaction (rs80198067; $p=9.9x10-5$), which was mostly driven by SZ ($p=6.3x10-4$); less by MDD ($p=2.3x10-2$) or BD (p=0.40). ANKRD46 encodes a protein containing multiple ankyrin repeat domains that is highly expressed in frontal cerebral cortex.
Conclusions: Further investigation of these loci showing SNP-by-sex interaction within/across disorders will be important for understanding the interactions between sex, genes, and neuropathophysiology that are shared/unshared across disorders.
Supported By: Other
Keywords: Genotype-by-Sex Interaction, Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Genome-Wide Interaction Study

T227. Using Gene Expression Maps to Contrast Different Brain Disorders and Traits

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Background: Genome wide association studies (GWAS) have associated single nucleotide polymorphisms (SNPs) with several brain disorders and traits. However, the brain expression patterns of the genes associated with these SNPs are poorly understood. Thus, we mapped existing gene expression data to a brain template for gene sets associated with schizophrenia (SCZ), attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease (AD), and examined associations between them.
Methods: We used mRNA expression data from 6 donors from the Allen Human Brain Atlas. Full-brain voxel-wise expression maps were created for each gene. GWAS summary statistics for SCZ, AD, ADHD, and educational attainment (EA) were used to extract whole-genome significant SNPs and annotated these to genes by means of linkage disequilibrium (LD) binning. Average voxel-wise expression maps were calculated based on the p-value of a given SNP, its distance to a gene, and LD; resulting in each phenotype being represented by a single expression map. Furthermore, a phenotype×phenotype correlation matrix was created based on calculated expression maps.
Results: Analysis of brain expression maps revealed that SCZ had the strongest correlations with the other phenotypes. SCZ was negatively correlated with ADHD (r=-0.60), and positively correlated with EA (r=0.55) and AD (r=0.38).
Conclusions: Assessing the spatial distribution of expression patterns for genes implicated in brain disorders may provide a novel approach to increase our understanding of the distinct and shared mechanisms across different brain disorders and traits. For example, our results indicate that the genetic contribution to SCZ and ADHD are spatially non-overlapping.
Keywords: Gene Expression, GWAS, Psychiatric

T228. Identifying Key SNPs and Pathways Underlying Cognition, Education and Schizophrenia

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Background: Prior investigation of the genetic architecture of educational attainment and schizophrenia has reported a counter-intuitive positive genetic correlation between these phenotypes. We sought to understand the differential genetic correlation that exists between those of cognition and education on schizophrenia.
Methods: LD-score regression (LDSC) was conducted to examine genetic correlations between schizophrenia, education, and cognition. SNPs nominally associated (p<.05) with education, but not cognition (p>.50), and vice-versa were selected. Follow-up pathway analysis was conducted to identify potentially associated biological pathways.
Results: Significant genetic correlations were found for i) cognition and schizophrenia (rg = -.192, p = 2.85e-10) ii) education and schizophrenia (rg = .097, p = 3.91e-5). The counter-intuitive positive correlation between education and schizophrenia was driven by SNPs unrelated to cognition (rg [scz] = .55, p = 1.06e-7). Inverse correlation between cognition and schizophrenia was accounted for by the cognition-specific SNPs (rg[scz] = -.11, p = 4.65e-2). Top enriched pathways for SNPs specific to cognition appeared to be ion transport and ion channel regulation, while those for education pointed to cell adhesion and neuronal developmental pathways.
Conclusions: In schizophrenia, ion transport and ion channel regulation related pathways appear dysregulated, explaining the strong negative genetic correlations with cognition. However, a subset of pathways related to cell adhesion and neuronal development underlying education appears to drive the counter-intuitive positive genetic correlation with schizophrenia. These findings suggest that neurodevelopmental abnormities implicated in schizophrenia may be associated with educational success in the general population, perhaps providing a mechanism of balancing selection for these seemingly deleterious alleles.
Supported By: R01; P50
Keywords: Cognition, Education, Schizophrenia, GWAS, Genetic Correlation

T229. Chromosome 21 Duplication and Cognitive Deficit in Schizophrenia

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Background: Studies have shown that specific copy number variants (CNVs) are associated with schizophrenia. Schizophrenia is a mental disorder that is frequently co-morbid with cognitive deficit. Overexpression of DYRK1A gene, located on chromosome 21, is a potential genetic contributor to the cognitive defect in Down syndrome. In this study, we investigated chromosome 21 duplications in schizophrenia patients and their association with cognitive dysfunction.
Methods: We recruited 268 schizophrenic patients from the Centre for Addiction and Mental Health. The Mini-Mental Status Examination (MMSE) was used to measure cognitive functioning. Genotyping was completed using Illumina Omni 2.5. Chromosome 21 CNV analysis was performed using SNP and Variation Suite (SVS) version 8 (Golden Helix). We compared the association between duplication and cognitive dysfunction using a chi-squared test. The total number of duplications between participants with and without cognitive deficits was compared using Mann Whitney U test (SPSS version 24).
Results: The mean MMSE score in our sample was 28.48 ± 2.12. Approximately, 50% of our subjects have duplication(s) in chromosome 21. Our preliminary CNV analysis did not show a significant association between duplication in chromosome 21 and cognitive deficit in our sample.
Conclusions: CNVs in the form of gene duplication are a source of evolutionary change, generating protein diversity, increases in gene dosage, and evolution of new functions. Although our results did not show a significant association between duplications in chromosome 21 and cognitive deficit, CNV studies of impairment in cognitive development may reveal important, novel insights, and open further investigation for the treatment of neuropsychiatric diseases.
Supported By: Dr. Vincenzo De Luca is supported by CIHR and AFSP.
Keywords: CNV, Cognitive Deficits, Schizophrenia

T230. Polygenic Risk Score Increases Schizophrenia Liability Through Cognition-Relevant Pathways: Causal Modelling With Latent Cognition and Polygenic Risk

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Background: Cognition shares substantial genetic variance with schizophrenia, with recent evidence from GWAS data and from modeling of twin data suggesting direct causality from the former to the latter. However, it is not clear how much of the genetic component of schizophrenia is mediated through cognition. Thus, we included in causation models direct measurements of the genetic risk (e.g. schizophrenia polygenic risk) to quantify the genetic component of schizophrenia that is mediated by cognition and captured by the polygenic risk.
Methods: Data were from 1,313 members of 1,078 families, and included 416 schizophrenia patients, 290 unaffected siblings, and 607 controls. Polygenic risk (PRS) were based on the latest data from the PGC and represented the sum of genotypic scores for all common genetic variants associated with schizophrenia. Cognition (L-COG) was extracted through common pathway models and captured the common variance across measurements in six cognitive domains.
Results: Of the genetic component of schizophrenia, 2.71% was through PRS pathways mediated by L-COG, 3.93% by PRS covariation pathways that included L-COG, and 26.87% by L-COG pathways not captured by the PRS. The remaining variance in schizophrenia liability was through pathways other than cognition and PRS.
Conclusions: Cognition pathways captured by the PRS score mediated a significant part of genetic risk for schizophrenia. However, the evidence suggests that other cognition pathways not captured by PRS mediate an even greater part. We anticipate that when schizophrenia PRS include all possible variants associated with risk, more than 25% of the variants' cumulative effect will first influence variation in cognition.
Supported By: X.Z. was funded by T.T. and P.S. through State Key Laboratory of Brain and Cognitive Sciences funds and an NIH subcontract (NIH-260850043) awarded to T.T. The data collection was funded by the intramural research program of the NIMH to the D.W.'s lab.
Keywords: Polygenic Risk Score, Schizophrenia, Cognition, Data Modelling

T231. Reduced Resting-State Functional Connectivity Between Cerebellar Lobules and Cortical Regions in Individuals With Schizophrenia

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Background: Reduced resting-state functional connectivity between the cerebellum and cortex has been demonstrated in individuals with schizophrenia. However, most research has focused on specific regions, leaving out the broader context of cerebello-cortical connectivity. Therefore, this study investigated connectivity between individual lobules and the whole brain; we started with the left cerebellum to examine dysfunctions in the right cortex in schizophrenia, which have been a point of contention. Relationships with polygenic risk scores (PGRS) were also explored.
Methods: Eighty-five healthy controls and 73 individuals with schizophrenia underwent resting-state scans and genotyping. Imaging data were preprocessed using a standard pipeline. Resting-state functional connectivity was calculated between 10 left cerebellar lobules and the whole brain. Group differences in connectivity between each lobule and the rest of the brain were computed. Relationships between PGRS (calculated using PRSice) and connectivity were tested for main effects and group x PGRS interactions.
Results: Controls demonstrated stronger connectivity between 7 cerebellar lobules and cortical regions. Significant connectivity differences were observed in the right parietal lobe, and to a lesser extent, frontal and temporal regions. PGRS did not predict cerebellar connectivity in either the control or schizophrenia group, but at the trend level higher PGRS score predicted lower cerebellar-cortical connectivity in several lobules.
Conclusions: Reduced connectivity between cerebellar and cortical regions in the schizophrenia group supports the cognitive dysmetria theory, suggesting weaker regionally specific cerebellar-cortical connectivity in schizophrenia. Though the current dataset was likely too small to detect significant relationships, trends suggest greater genetic risk for schizophrenia may predict reduced cerebellar connectivity.
Supported By: NIH/NIGMS P20GM103472; Georgia State University Neurogenomics 2CI Fellowship
Keywords: Schizophrenia, Functional Connectivity, Cerebellum, Polygenic Risk Score

T232. Abnormal Thalamocortical Functional Connectivity Correlates With Sleep Spindle Deficits in Schizophrenia

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Background: A growing literature implicates abnormal thalamocortical circuitry in the pathophysiology of schizophrenia. Resting state functional connectivity MRI (rs-fcMRI) studies consistently report increased thalamic connectivity with sensorimotor cortex both in schizophrenia patients and in individuals at high risk, in whom it predicts conversion to psychosis. We examined the relation of thalamocortical functional connectivity to sleep spindles, defining EEG oscillations of non-rapid eye movement stage II sleep (N2) that are initiated in the thalamic reticular nucleus (TRN), depend on

thalamocortical feedback loops for their expression and are reduced in schizophrenia.
Methods: Twenty-two chronic medicated schizophrenia patients and 29 demographically-matched healthy controls completed a study that involved overnight polysomnography to measure N2 sleep spindle density (number per minute) and rs-fcMRI. Subject-based analysis of functional connectivity between the thalamus seed and cortex was implemented in CONN. Group comparisons of thalamocortical connectivity and its relation to spindles were conducted with PALM and corrected for multiple comparisons with a clustering algorithm.
Results: We replicated previous findings of decreased spindle density and increased thalamic connectivity with sensorimotor cortex in schizophrenia. These two abnormalities were significantly correlated, consistent with the hypothesis of a common underlying mechanism.
Conclusions: We propose that both thalamic hyperconnectivity and spindle deficits in schizophrenia reflect reduced TRN-mediated inhibition. The TRN is the major inhibitory nucleus of the thalamus. It gates the relay of sensory information to cortex and initiates sleep spindles. Postmortem studies show TRN abnormalities in schizophrenia that may contribute both to increased, but less filtered, forwarding of information to the cortex and to spindle deficits.
Supported By: R01MH092638; K24MH099421; R01MH048832
Keywords: Thalamus, Thalamic Reticular Nucleus, Resting-State Functional Connectivity, Schizophrenia, Sleep Spindles

T233. Obesity and Brain Age in First Episode of Schizophrenia-Spectrum Disorders – Effects of Antipsychotic Medications

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Background: Neuroanatomical alterations are common in schizophrenia, but their origins remain poorly understood. Obesity is frequent in schizophrenia, may be associated with exposure to antipsychotics and with brain structural changes similar to those found in psychosis. Yet, it is unclear whether metabolic alterations contribute to brain changes in schizophrenia or even mediate the negative effects of antipsychotics on brain structure.
Methods: We acquired 3T brain structural MRI in 124 participants with first episode of schizophrenia (FES), during their first psychiatric hospitalization and 114 controls. We also calculated body mass index (BMI) at admission and at the time of scanning. We used machine learning to estimate the individual brain age and calculated the BrainAGE score by subtracting the chronological from the estimated brain age.
Results: BrainAGE scores were additively associated with FES and obesity/overweight ($R2=0.20$, $p<0.001$). BrainAGE scores in previously medication-naïve participants ($N=39$) were lower than in controls ($F(1,150)=8.82$, $p=0.003$) and, comparable to previously medicated FES individuals ($F(1,121)=0.15$, $p=0.70$). At admission, FES participants had comparable BMI to controls ($t(150)=0.53$, $p=0.60$). Although BMI increased during the hospitalization ($t(115)=-2.87$, $p=0.004$), BrainAGE scores were associated even with BMI measured at admission ($r(114)=0.18$, $p<0.05$), but not with exposure to antipsychotics.
Conclusions: Overweight/obesity may be an independent risk factor for brain alterations already in FES. The contribution of medications to these findings was less likely, as BrainAGE scores were found already in recently medication naïve participants and BrainAGE scores negatively correlated with BMI measured already at admission. Targetting overweight/obesity might slow brain ageing in FES.
Supported By: Dr. Hajek received funding for this study from Canadian Institute of

Health Research (grant #341717), Brain and Behavioral Research Foundation (Independent Investigator Award), the Ministry of Health, Czech Republic (F.S., grant number 16-32791A). The National Institute of Mental Health, Klecany, Czech Republic was supported by project Nr. LO1611 with funding from the MEYS under the NPU I program. Dr. Franke was supported by German Research Foundation grant [DFG; Project FR 3709/1-1 to KF].
Keywords: Obesity, Brain Aging, Antipsychotics

T234. Parsing Heterogeneity in Schizophrenia Using Inter-Subject Variability in Multimodal Neuroimaging Phenotypes

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Background: The clinical diagnosis of schizophrenia is thought to define groupings of patients with heterogeneous pathophysiology. Neuroimaging offers the most direct method for assessing schizophrenia-related heterogeneity in brain structural and functional measures. Here we used inter-subject correlation (ISC) scores to measure heterogeneity in functional and structural brain imaging phenotypes in patients schizophrenia compared to healthy individuals.
Methods: We computed individual inter-subject correlation (ISC) scores based on measures of subcortical volume, cortical thickness, within- and between- network resting-state functional connectivity, and working memory (WM)-activation in 100 patients with schizophrenia and 50 healthy individuals. For the patients only, we also computed a normative ISC score (ISCn) representing the degree of correlation between each patient and the healthy group. We tested the effect of diagnosis, demographic and clinical features on ISC.
Results: Compared to healthy individuals, patients had reduced ISC in WM-activation ($p=2.10-6$) and cortical thickness ($p=0.04$), suggesting that the patients had a less

homogeneous profile. The ISC and ISCn scores were highly correlated for all neuroimaging phenotypes (r>0.47), suggesting that patients who were more similar to healthy individuals also had a more homogeneous profile. In healthy individuals, higher IQ and lower body mass index were positively associated with ISC in WM-activation and in cortical thickness. In patients, higher IQ was associated with higher ISCn in WM-activation (r=0.24, p=0.03).
Conclusions: We demonstrate that measures of WM activation and cortical thickness show the highest degree of heterogeneity in patients schizophrenia and this heterogeneity is closely associated with general cognitive ability.
Supported By: R01 MH104284-01A1
Keywords: Schizophrenia, Multimodal Imaging, MRI Brain Imaging, Inter-Subject Variability

T235. Brain Abnormalities in Cotwins, Siblings, Offspring and Parents of Schizophrenia and Bipolar Patients: An ENIGMA Collaboration

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Background: First-degree relatives of schizophrenia (SZ) and bipolar disorder (BD) patients show brain abnormalities. Through the ENIGMA consortium, we compared different types of SZ or BD first-degree relatives (i.e., cotwins, siblings, offspring, parents) to controls on global and subcortical brain measures.
Methods: To date, 6,235 individuals from 30 independent studies were included. MRI scans were processed with FreeSurfer. Linear mixed model analyses were performed comparing each type of relative to controls. Cohen's d effect sizes were obtained at each site and then pooled using an inverse variance-weighted random-effects meta-analysis for all relatives combined.
Results: BD relatives had significantly larger ICV, lateral ventricle, cortical and cerebellum gray matter (GM) volumes and surface area (d's≥0.12) compared to controls. Only smaller thalamus volume (d=-0.13) was found after correction for ICV.

SZ relatives showed significantly smaller volumes of total brain, cerebral white matter (WM), cerebellar GM and WM, cortical thickness, accumbens, putamen and thalamus (d's≤-0.09), and larger third ventricle volume (d=0.13) compared to controls. The findings for SZ relatives remained largely similar or effect sizes increased after ICV correction, and additionally included smaller cortical GM volume (d=-0.13).
Conclusions: BD relatives have a larger ICV compared to controls, which was not the case in SZ relatives. In contrast, smaller brain volumes were present in SZ relatives. This may implicate that familial risk for SZ and BD differentially associates with brain structure, possibly reflecting different neurodevelopmental pathways. We are currently analyzing whether psychopathology in the relatives explains our findings, and whether there are differences between the different types of relatives.
Keywords: Schizophrenia, Bipolar Disorder, First-Degree Relatives, sMRI, Meta-Analysis

T236. Reduced Integrity of Transcallosal Auditory Fibers and Auditory Hallucinations in the First Episode Schizophrenia Spectrum

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Background: Auditory verbal hallucinations (AVH) are common in schizophrenia, even early in course. Connectivity between left and right auditory cortex may be related to AVH via impaired information transfer and coordination. Transcallosal auditory cortex connectivity in first-episode schizophrenia individuals (FESz) at first clinical contact was examined.
Methods: Twenty-nine FESz and 23 matched (age, sex, IQ, pSES) healthy controls (HC) underwent diffusion spectrum imaging (DSI). Fourteen FESz heard voices (AVH+), 15 did not (AVH-). A deterministic fiber tracking algorithm identified fibers passing through the posterior third of the corpus callosum and ending bilaterally in Brodmann's area 22, Heschl's gyrus, or planum temporale. Connectivity was compared between groups for tract volume, generalized Fractional Anisotropy (gFA), and isotropy.
Results: MANOVA revealed group differences in tract volume ($p = .039$) and gFA ($p = .013$). Within FESz, AVH severity significantly correlated with auditory cortex transcallosal gFA ($r = -.44$, $p = .013$). Pairwise t-tests indicated lower gFA and greater tract volume for AVH+ vs AVH- ($p's < .05$). HCs had a trend towards greater gFA ($p = .068$) vs AVH+ and tract volume ($p = .063$) vs AVH-. All other comparisons were nonsignificant ($p > .1$).
Conclusions: Altered structural connectivity contributes to AVH in schizophrenia, even early in disease course. Reduced gFA in FESz correlated with AVH severity, suggesting that inefficient coordination of left and right hemisphere auditory processing, crucial for language, may indicate a biological AVH subtype. Current work is examining transcallosal integrity across Kraepelinian diagnostic categories (e.g., bipolar disorder and depression with psychotic features).
Supported By: NIH P50 MH103204, R01 MH113533
Keywords: First Episode Psychosis, Auditory Cortex, Structural Connectivity, Auditory Hallucinations, Diffusion Spectrum Imaging

T237. Parahippocampal Gray Matter Thickness, Verbal Fluency, and Auditory Hallucinations in the First Episode Schizophrenia Spectrum

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Background: Progressive gray matter decrease is present in the prodromal and early post-psychosis course of schizophrenia. Medial and left lateral temporal areas appear to be particularly affected. However, it remains unclear what structures are impacted first and how these abnormalities relate to symptom severity and cognitive functioning. Therefore, we examined first episode schizophrenia-spectrum individuals (FESz) at first contact with psychiatric services.
Methods: T1-weighted MRI scans were acquired on 29 first-episode (FESz) and 32 matched healthy control (HC) individuals. Cortical thickness was estimated for 35 bilateral ROIs (Desikan-Killiany atlas) using Freesurfer. A cluster-based permutation test was used to determine significant group differences. Symptoms were rated with the Positive and Negative Syndrome Scale. Participants completed a category fluency task, naming as many animals as they could in one minute.
Results: FESz displayed significant decrease in left fusiform gyrus, right insula, and right parahippocampal gyrus thickness ($p<.05$). Decreased parahippocampal gyrus thickness in left ($r=.39$, $p<.05$) and right ($r=.37$, $p<.05$) hemispheres were associated with worse verbal fluency. Increased right parahippocampal gyrus thickness was significantly associated with increased hallucinations ($r=.40$, $p<.05$).
Conclusions: Right parahippocampal, right insula, and left fusiform gyrus thickness appear smaller in FESz. Parahippocampal gyrus thickness is associated with verbal fluency and hallucinatory behavior in FESz. This may reflect the role of the parahippocampal gyrus in verbal memory, disorders of which may impact hallucinatory behavior and language deficits in schizophrenia very early in disease course, as parahippocampal volume is also reduced in high risk patients that convert to psychosis.
Supported By: P50 MH103204, R01 MH113533, and 5T32 NS007433-20
Keywords: Schizophrenia, First Episode Schizophrenia, Gray Matter Thickness

T238. Antipsychotic Treatment and the Basal Ganglia: A Structural MRI Study

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Background: MRI studies demonstrate morphological brain changes after antipsychotic treatment, but the mechanism is unknown. We investigated if basal ganglia volumes differ by treatment status in psychosis and bipolar disorders. We hypothesized an association with dosage, remission status and estimated receptor occupancy.
Methods: FreeSurfer was used to segment the putamen, caudate nucleus and globus pallidus (GP) of 224 patients with psychotic or bipolar disorders treated with antipsychotics; 26 previously treated, 29 never treated and 301 healthy controls (HC) from the TOP cohort (NORMENT). ANCOVA and linear regression models, adjusting for age, gender and ICV, were used. Seed-based analysis of structural covariance with vertex-wise cortical thickness was performed.
Results: The currently medicated patients predominantly used atypical antipsychotics. We found larger right putamen ($p=0.003$), left ($p=0.02$) and right GP ($p=0.03$) in currently medicated patients compared to HC. Higher current chlorpromazine equivalent dose (CPZ) was associated with larger left GP ($p=0.04$). Remission and estimated receptor occupancy ($n=47$) were not associated with subcortical volumes. There was lower positive correlation between left putamen and left lateral occipital cortex in medicated patients compared to HC. No other differences in structural covariance were found
Conclusions: The results replicate previous findings indicating a medication-induced effect. Causality could not be determined since the study was observational and confounding cannot be ruled out. The hypothesized association between basal ganglia volumes and estimated receptor occupancy was not supported, but a dose-response relationship in GP was observed. Further studies are needed to clarify how pharmacological properties of antipsychotics relate to brain morphology.
Supported By: The Research Council of Norway; K.G. Jebsen Foundation; South-Eastern Regional Health Authority, Norway.
Keywords: Pharmacology, Psychotic Disorders, MR Structural Imaging, Basal Ganglia

T239. Validation of an Instrument Assessing State and Trait Auditory Hallucinations: From Psychometrics to Brain Connectivity

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Background: Auditory hallucinations (AH) are a cardinal symptom of schizophrenia, typically assessed using "state" measurements of current severity. Longitudinal "trait" measurements of lifetime severity are a developing concept; however, valid tools are lacking. We developed a novel scale assessing state and trait auditory perceptual disturbances and hallucinations, then performed psychometric and neuroimaging tests for initial validation.
Methods: Schizophrenia patients (SZ, $n=205$) and community controls (CC, $n=202$) completed the novel 24-item scale. Exploratory factor analysis was used to identify subscales, which were assessed for reliability and validity. Resting-state functional connectivity analyses in SZ ($n=65$) employed a left temporal-parietal (ITPJ) seed implicated in AH, to identify neural correlates of the auditory subscales.
Results: Factor analyses revealed three subscales in SZ: lifetime auditory disturbances and hallucinations (Trait-ADH),

current subclinical auditory disturbances (State-AD), and current auditory hallucinations (State-AH). These were not observed in CC. In SZ, subscales showed good reliability, and good convergent and divergent validity. Neuroimaging analyses identified several regions ($p<0.05$ corrected) showing connectivity associated with distinct subscales. Notably, Trait-ADH was positively associated with lTPJ-insula/heschls gyrus (HG) connectivity, but negatively associated with lTPJ-dorsal lateral prefrontal (dlPFC) connectivity. Furthermore, significant moderation was observed: the positive association for lTPJ-insula/HG connectivity was attenuated by high lTPJ-dlPFC connectivity.

Conclusions: This work highlighted novel assessment of lifetime auditory hallucinations, with results supporting use of this scale in future research and clinical care. We also demonstrated that the predisposition to these symptoms in SZ may in part be driven by aberrant interactions between bottom-up and top-down resting-state connectivity with the TPJ.

Supported By: This work was supported by the National Institutes of Health (grant numbers R01MH112180, U01MH108148, R01EB015611, P50MH103222, T32MH067533, K23MH112010), a State of Maryland contract (M00B6400091), and a National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD) Young Investigator Award from the Brain and Behavior Research Foundation.

Keywords: Schizophrenia, Auditory Hallucination, Assessment, Resting-State Functional Connectivity

T240. Relationship Between Cognitive Performance and Superficial White Matter Integrity in the Cingulate Cortex in Schizophrenia: A DWI Study Using a Novel Atlas

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Background: Evidence is mounting to suggest that changes in superficial white matter (SWM) U-shaped short-range fibers are integral components of schizophrenia neuropathology, a theory that is supported by findings from postmortem studies and less often in vivo in patients with SZ. This diffusion weighted imaging (DWI) study aimed to investigate SWM in people with SZ and to determine its relationship with cognition.

Methods: Whole brain tractography was performed in 31 people with SZ and 54 healthy controls. Segmentation and labelling of superficial white matter tracts were performed using a novel atlas characterizing 100 bundles. Cognition in the domains of working memory and verbal comprehension were assessed.

Results: Fractional anisotropy (FA) was significantly reduced in multiple bundles throughout the frontal cortex in people with schizophrenia as compared with healthy controls. The greatest effect was seen in the cingulate cortex, which was strongly associated with measures of working memory ($r = 0.51$, $p < 0.01$) and verbal comprehension ($r = 0.56$, $p < 0.01$).

Conclusions: Our results support neuroimaging and neuropathological findings of alterations in SWM the frontal lobe in people with SZ. Moreover, we replicate previous findings of a relationship between FA in the anterior cingulate and cognitive performance in SZ. Identifying patterns of superficial white matter dysconnectivity may be helpful in understanding the prominent symptoms and cognitive deficits and observed in SZ.

Supported By: Fondation Fondamental, Marie Curie

Keywords: Schizophrenia, White Matter Integrity, Diffusion Imaging, Cognition

T241. Neural Mechanisms of Presence Hallucination and Passivity Experience Induced by Sensorimotor Conflicts in Healthy Subjects: A Robotics-fMRI Study

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Background: Deficits in self-monitoring, where comparisons between the sensory outcomes of actions and their predicted consequences are impaired, have been proposed to lead to abnormal bodily experience, hallucinations and psychosis. In line with this theory, recent findings demonstrated that robot-controlled sensorimotor conflicts between upper limb movements and somatosensory feedback on the back are able to induce psychosis-like sensations in healthy subjects. Such states include the presence hallucination (PH), i.e. the sensation that someone is nearby when actually no one is present, and passivity sensations.

Methods: We investigated the brain mechanisms underlying these two psychosis-related states in 16 healthy subjects. To this purpose, we relied on an MR-compatible robotic system able to generate the aforementioned sensorimotor conflicts,

and thereby inducing PH and passivity experience, while recording resting state and task-related brain activity using fMRI.
Results: We initially validated that our robotic system could reliably activate motor and sensory regions, and reproduce the PH and passivity experience. An extended cortical network composed of the bilateral insula and temporo-parietal junction and subcortical areas including the thalamus and the basal ganglia, were more activated in the sensorimotor condition associated with PH. Results from the resting state analysis showed that connectivity between specific somatosensory-premotor regions could predict the strength of PH and passivity sensations, indicating that that disconnections between those areas were associated with higher psychosis-like states.
Conclusions: Collectively, these robotically-induced findings shed new light on the neural correlates of mild psychosis sensations in healthy subjects, thereby advancing the scientific understanding of symptomatic hallucinations and psychosis in psychiatry.
Supported By: National Center of Competence in Research (NCCR) "SYNAPSY – The Synaptic Bases of Mental Diseases"
Keywords: Neuroimaging, Robotic Stimulation, fMRI, Resting-State fMRI, Hallucinations

T242. Genetic Risk Loading for Schizophrenia, Bipolar Disorder, and Major Depression and Hippocampal Subregion Volumes

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Background: Severe mental disorders, including schizophrenia, bipolar disorder and depression have subregion-specific effects on the hippocampal volume. Given that hippocampal volumes are heritable, we hypothesized that, in healthy subjects, polygenic risk scores (PRS) for these disorders could partially explain hippocampal subregion volumes.
Methods: Participants were 1123 healthy individuals of European ancestry from the Brain Genomics Superstruct Project (mean age = 21.3±3.0, 54% females). Seven hippocampal subregion volumes were measured in T1-weighted images using Freesurfer 6.0. We calculated PRS for three disorders using 8 different statistical thresholds based on GWAS results from the PGC, ICCBD, and SSGAC consortiums (focused on schizophrenia, bipolar disorder and depressive symptoms, respectively). The effects of PRS on subregion volumes were estimated using linear models controlling for potential confounds.
Results: PRS for schizophrenia had a negative effect on left subiculum volume (peak at $P < 10^{-4}$, p-value = .008) and left presubiculum volume (peak at $P < 10^{-4}$, p-value = .007). PRS for bipolar disorder had a positive effect on left CA2/3 (peak at $P < .01$, p-value = .007) and dentate gyrus (peak at $P < .01$, p-value = .007) volumes, respectively. PRS for depressive symptoms had no significant effects on subregion volumes.
Conclusions: PRS for schizophrenia and bipolar disorder showed distinct associations with volumes of specific subregions of the hippocampus in healthy individuals. Although these effects are modest, they are in line with earlier studies showing that these regions are affected by schizophrenia and bipolar disorder. These findings require replication in an independent sample.
Keywords: Polygenic Risk Score, Hippocampus, Schizophrenia, Bipolar Disorder, Depression

T243. Whole-Brain Functional Connectivity-Learning Relationships in Schizophrenia

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Background: Learning difficulties strongly relate to functional outcome in schizophrenia. Although aberrant functional connectivity (FC) has been shown to underlie various cognitive impairments in the disorder, less work has examined how this dysconnectivity relates specifically to the instantiation of learning. Many whole-brain FC studies showing dysconnectivity in schizophrenia have used resting-state studies. Our study aims to further the understanding of whole-brain FC by examining the direct relationship to performance on a learning task over multiple days.
Methods: Twelve healthy volunteers and 12 volunteers with schizophrenia completed two fMRI scanning sessions over 1 week. In-scanner performance on a lexicon-learning task cross-correlated with pairwise FC in regions across the entire brain was examined using data-driven multivariate PLS analysis. Resampling statistics were used to determine the significance and reliability of the results.
Results: Whole-brain FC-learning patterns characterized early and late network shifts for the healthy participants with increased correlation of prefrontal-thalamic networks and decorrelation of middle-temporal networks with performance. These patterns were absent or weaker in the schizophrenia group. In contrast, a dominant time-invariant FC-learning pattern showed the impact of persistent aberrant intra-cerebellar and cerebellar-frontal network connectivity on learning performance in schizophrenia.
Conclusions: These results are consistent with earlier studies showing distributed aberrant FC incorporating thalamic and cerebellar nodes in schizophrenia. Here, we extend this finding to show the direct impacts of this dysconnectivity pattern on learning performance. Furthermore, our results suggest that, in schizophrenia, less dynamism in network rearrangement over the course of learning interferes with learning accuracy.
Supported By: This work was supported by a JS McDonnell Foundation Grant (220020255) to A.R. McIntosh and a CIHR Operating Grant to S. Kapur.

Keywords: Brain Functional Connectome, Multivariate Analysis, Schizophrenia, Task fMRI, Cognitive Neuroscience

T244. Neurochemistry in the Medial Prefrontal Cortex in Medication-Naïve First Episode Psychosis and Response to Antipsychotic Treatment

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Background: Understanding the underlying neurobiology present in the early stages of schizophrenia is a pivotal step in designing targeted interventions. A number of studies have reported alterations in neural integrity and glutamatergic transmission. Importantly, a cross-sectional study suggested that glutamate levels in the medial prefrontal cortex (MPFC) are elevated in unmedicated, but not in medicated patients. However, no studies have prospectively investigated effects of antipsychotic treatment.
Methods: We included 21 medication-naïve FEP and 22 controls in this longitudinal study. Symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS); treatment response was calculated as the change in positive symptom severity after 16 weeks of treatment. Spectra were obtained from a bilateral MPFC voxel (PRESS; TR/TE= 2000/80ms) and quantified in jMRUI (with respect to creatine and to internal water).
Results: Mean age of FEP was 22.73 years, 64% were male. Mean age of controls was 22.95 years, 62% were male. 16 FEP completed the study. At baseline, none of the metabolites differed between groups. We also did not find any changes in metabolites after sixteen weeks of treatment. N-acetyl-aspartate/Creatine (NAA/Cr) at baseline significantly correlated with response to antipsychotic treatment.
Conclusions: We report no neurometabolite abnormalities in the MPFC in FEP and no changes in measures after 16 weeks of treatment. None the less, our data suggests that greater neural integrity at baseline, expressed by NAA/Cr, is associated with better response to treatment. This suggests that the brain may be "wired" in a way that does or does not favor response to antipsychotic treatment.
Supported By: R01MH102951
Keywords: Schizophrenia, Drug-Naive, First Episode Psychosis, Neuroimaging, Magnetic Resonance Spectroscopy

T245. Antipsychotic Medications do not Affect Abnormal Extracellular Free Water and Spatial Configuration of Neurites in Unmedicated Patients With Schizophrenia

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Background: Only few studies have used advanced diffusion models to characterize white matter abnormalities in schizophrenia, and none have examined effects of antipsychotic treatment on these measures.
Methods: We enrolled 42 unmedicated patients with schizophrenia and 42 matched controls. DTI data (in plane resolution 2.2mm, slice thickness 2.2mm, 30 directions x2, b-value 1000 s/mm2, 5 b0 images) were obtained before and after six weeks of treatment with risperidone. Data were preprocessed in TORTOISE and the NODDI toolbox was used to generate extracellular free water and orientation dispersion index maps. To assess whole brain voxel-wise group differences and changes over time in diffusion indices we used AFNI's 3dttest++ (age, sex, and relative motion as covariates) with clustsim to correct for multiple comparisons.
Results: At baseline, voxelwise analyses demonstrated increased extracellular free water in the hippocampal part of the cingulum and decreased extracellular free water in the brainstem, as well as increased orientation dispersion in the external capsule. Whole brain white matter extracellular free water was significantly increased in patients compared to controls ($p = .03$). Longitudinal analyses showed no changes in whole brain extracellular free water or orientation dispersion in patients after six weeks of treatment with risperidone.
Conclusions: Using advanced diffusion models, we report alterations in both extracellular free water and spatial configuration of neurites in unmedicated patients with schizophrenia. Our data suggests that a short term course of antipsychotic medication may not alter white matter microstructure, but studies with longer follow up durations will be important to determine long term effects of antipsychotic medications.
Supported By: NIMH R01MH081014 and R01MH102951, ACL; K23MH106683, NVK
Keywords: Extracellular Free Water, Antipsychotics, Schizophrenia, Longitudinal Brain Imaging, Diffusion Imaging

T246. Low Availability of the α7 Nicotinic Acetylcholine Receptor Distinguishes Recent Onset of Non-Affective Psychosis From Affective Psychosis: A Study Using [18F]ASEM PET

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Background: A major challenge to clinical management of early psychosis is difficulty in discriminating non-affective psychosis (NP) from affective psychosis (AP) at time of first presentation. Nicotinic signalling through the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$-nAChR), may provide such a differentiating biomarker. The uniquely low availability of the $\alpha 7$-nAChR in the hippocampus in NP may also mark a discriminating etiology of the hippocampal dysfunction in NP versus AP, with implications for early diagnosis, therapy, and fundamental understanding of psychosis.
Methods: Patients with recent (within five years) onset of NP (Schizophrenia, Schizoaffective Disorder) or of AP (Bipolar I Disorder), and well-matched healthy controls (HCs) completed positron emission tomography (PET) with [18F]ASEM.

Participants were non-smokers. Treatment was restricted to current monotherapy (lithium, atypical antipsychotic) or no medication. Participants also underwent neuropsychological testing and structural neuroimaging. Total distribution volume (VT) in hippocampus was estimated using Logan analysis with metabolite-corrected arterial input function.
Results: A one-way ANOVA with three groups (NP, AP, HC) revealed significant group effect on VT in hippocampus. Secondary analysis controlling for age did not change the results. A Tukey post hoc test revealed lower [18F]ASEM VT in hippocampus in NP compared to HC or AP, and results remained unchanged after partial volume correction. [18F]ASEM VT in hippocampus positively correlated with Hopkins Verbal Learning Test scores among the combined patient cohorts, but not among HCs.
Conclusions: These [18F]ASEM PET data are consistent with low hippocampal α7-nAChR availability in NP relative to that in AP or HCs, and suggest its relationship to cognitive impairment in psychosis.
Supported By: A Johns Hopkins Doris Duke Early Clinician Investigator Award; The Alexander Wilson Schweizer Fellowship, A Johns Hopkins University Innovation Award; The Ryan Licht Sang Bipolar Foundation
Keywords: PET Imaging, [18F]ASEM, Recent Onset of Psychosis, Hippocampus, α7 Nicotinic Acetylcholine Receptor

T247. Oxytocin Gene Networks in the Human Brain: A Gene Expression and Large-Scale fMRI Meta-Analysis Study

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Background: Oxytocin modulates animal and human reproductive and social behavior, with implications for several psychiatric disorders. However, the therapeutic potential of oxytocin in mental health care suggested by animal research has not been successfully translated into clinical practice. This may be partly due to a poor understanding of the expression and distribution of the oxytocin signaling pathway in the human brain, and its complex interactions with other biological systems.
Methods: We characterized the full-brain distribution of OXT, OXTR, and CD38 mRNA — three oxytocin pathway genes frequently implicated in human social behavior — using post-mortem tissue from 6 donors, collected from the Allen Human Brain Atlas. Each brain was sampled in 363-946 distinct locations using a custom Agilent 8 $\times$ 60K cDNA array chip. In addition, we identified putative gene pathway interactions by comparing full-brain gene expression patterns across 20737 genes, and assessed associations between gene expression patterns and mental states via a large-scale fMRI meta-analysis (11,406 studies) using the NeuroSynth framework.
Results: OXT, OXTR, and CD38 expression was increased in central, temporal, and olfactory regions (FDR corrected p-values $<$ .05). Across the brain, there was high co-expression with several dopaminergic and muscarinic acetylcholine genes, reflecting an anatomical basis for critical gene pathway interactions. Finally, fMRI meta-analysis revealed that oxytocin pathway gene map locations correspond with regions associated with motivation and emotion processing (Spearman's r values $>$ .33).
Conclusions: These results provide a proof-of-principle demonstration of corresponding mental states with gene expression patterns of a neuropeptide pathway involved in complex human behaviors.
Supported By: Novo Nordisk Foundation; Research Council of Norway; KG Jebsen Stiftelsen Foundation; South-Eastern Norway Regional Health Authority.
Keywords: Oxytocin, mRNA, Gene Expression, Human Postmortem Brain, Emotional Processing

T248. Insulin Action and Cognition in Patients With First-Episode Psychosis

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Background: There is a disproportionately high rate of type 2 diabetes mellitus in patients with psychotic disorders compared to the general population, and glucose metabolism abnormalities are present at psychotic illness onset. Increasing evidence suggests that impaired insulin signaling leads to cognitive dysfunction. The present study examined the association between insulin action and cognitive function in patients with first episode psychosis.
Methods: 16 patients with first episode psychosis were recruited from the McLean Hospital OnTrack program for first episode psychosis. Participants underwent standard clinical assessments. Cognition was measured by the MATRICS Consensus Cognitive Battery (MCCB) and the MCCB composite total score. Participants were evaluated using a two-hour oral glucose tolerance test (OGTT), with 7 blood samples drawn for plasma glucose and serum insulin concentration measurements. Insulin sensitivity was quantified using the oral minimal model method. Lipid, leptin and inflammatory marker levels were also measured. All study procedures were approved by the McLean Hospital Institutional Review Board and participants provided written informed consent.
Results: The mean (SD) age was 24.1(3.3) years and mean (SD) body mass index (kg/m2) was 26.9 (3.9). The MCCB total composite score was significantly associated with insulin sensitivity ($r=0.56$, $p=0.023$).
Conclusions: These results suggest that insulin signaling may be a factor to consider in addressing cognitive deficits in early psychotic illness. As cognitive deficits are not adequately targeted with current treatment, future approaches to modulate

insulin signaling early in illness may offer the possibility of improving cognition in psychotic disorders.
Supported By: This research was supported by NIMH to Dost Öngür (R01MH094594 and K24MH104449) and Virginie-Anne Chouinard (5T32MH016259), and the Pope-Hintz Fellowship to Virginie-Anne Chouinard. This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102), financial contributions from Harvard University and its affiliated academic healthcare centers and the Intramural Research Program of the NIH, The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and DK-075116. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.
Keywords: Insulin, Cognition, First Episode Psychosis

T249. Theater Improvisation Training to Promote Social Cognition (TIPS): A Novel Recovery-Oriented Intervention for Youths at Clinical Risk for Psychosis

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Background: Individuals at clinical risk for psychosis (CR) consistently demonstrate social cognitive deficits. Theater training is designed to facilitate social communication and spontaneity. We evaluated the feasibility of theater improvisation training as a social cognition intervention in CR.
Methods: Thirty-six CR participants aged 15-25 years were ascertained from the Philadelphia Neurodevelopmental Cohort. Twenty-six completed the TIPS protocol: 18 weekly 2-hour small group theater sessions (n=8-12) led by a theater director and an actor-assistant. During sessions, participants engaged in collaborative acting and improvisation exercises. Baseline and follow-up assessments each included the Clinical Assessment Interview for Negative Symptoms (CAINS), Structured Interview for Prodromal Syndromes, and Penn Computerized Neurocognitive Battery (CNB) which includes social cognitive testing. Ten participants completed median 2.5 sessions but did not complete follow-up assessment. Longitudinal outcomes were analyzed using linear mixed models in R.
Results: There were no significant differences in baseline demographics, psychosis symptoms, or cognition between those who did and did not complete the TIPS protocol. Compared to baseline, CR participants at follow-up improved significantly on overall psychosis-spectrum symptoms as reflected by the total Scale of Prodromal Symptoms score (Coef=-5.8, p=0.01), as well as on the positive symptoms (Coef=-2.5, p=0.01) and negative symptoms subscales (Coef=-2.2, p=0.02). Global assessment of function scores also improved (Coef=6.3, p=0.003). There were no changes in scores for the CAINS or CNB.
Conclusions: TIPS is a recovery-oriented, non-stigmatizing and feasible intervention targeting social cognition and functioning in CR − a sensitive population with significant impairments and risk for serious mental illness. Further studies evaluating efficacy are indicated.
Supported By: R34 MH105248-01
Keywords: Clinical High-Risk States for Psychosis, Social Cognition, Early Intervention

T250. Schizophrenia Treatment With Single-Session tDCS and Cognitive Remediation Training: Preliminary Findings

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Background: Perceptual models of auditory verbal hallucinations (AVH) in schizophrenia (Sz) include hyper-excitability of auditory/verbal perception (in left temporoparietal junction; l-TPJ), and hypo-excitability of cognitive control which normally inhibits or reattributes perceptual misrepresentations (in right ventrolateral prefrontal cortex; r-VLPFC). We examined a single-session treatment to enhance cognitive control with Cognitive Remediation Training (CRT) plus anodal tDCS applied to r-VLPFC, and to reduce AVH with cathodal tDCS applied to l-TPJ.
Methods: Participants were 12 Sz with persistent daily AVH despite stable antipsychotic medication for >2 months. tDCS (2mA, n=7) or sham (0.1mA, n=5) was delivered during CRT. We assessed AVH at baseline and 1-week later. Participants also completed the AX-CPT during electroencephalography (EEG) testing at baseline and immediately after CRT+tDCS. We analyzed beta-band event-related desynchronization (ERD) during the cue evaluation period (200-400ms after 'A' stimulus onset) in left central electrodes, which has been linked to cognitive control of attention, and accuracy and RT.
Results: AVH was reduced by CRT+tDCS (36% reduction) compared to CRT+sham (18% reduction; d=0.82). In the AX-CPT, RT improvement was greater for CRT+tDCS (ΔRT=73ms) than CRT+sham (ΔRT=21ms; d=0.80). Beta ERD in the evaluation period was increased more for CRT+tDCS (ΔERD=0.49μV2) than CRT+sham (ΔERD=0.00μV2; d=0.89). Accuracy did not change for either group.
Conclusions: These preliminary results suggest that a single session of CRT+tDCS may reduce AVH severity and enhance cognitive control in treatment-refractory schizophrenia patients. These findings could lead to a new adjunct biomedical treatment for improving cognition and reducing auditory verbal hallucinations in schizophrenia.
Keywords: Electroencephalography (EEG), Transcranial Direct Current Stimulation (tDCS), Cognitive Control, Auditory Hallucination, Schizophrenia

T251. Severity of Impairment in Cognition and Negative Symptoms and Their Relation With Functional Deficits

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Background: Negative symptoms and cognitive impairments predict functioning in schizophrenia, with little research attempting to determine which levels of impairment are sufficient to predict functional deficits.
Methods: People with schizophrenia (n=632) were assessed with the MCCB and PANSS, and by high contact informants with the Specific Levels of Functioning scale (SLOF). Negative symptoms of reduced emotional experience were specifically targeted for analysis. We performed a median split on the total score for the emotional experience items and divided patients based on their MCCB global scores (not impaired vs impaired, at or below 1.0 SD below the population mean (T<40), then examined correlations between cognition, negative symptoms and everyday functioning in the groups with lower and higher negative symptoms and those with/without cognitive impairment.
Results: The severity of negative symptoms was correlated with SLOF interpersonal functioning in all patients, r=.42, p<.001, lower severity patients, r=.22, p<.001, and higher scoring patients, r=.31, p<.001. Negative symptoms did not predict the other two functional domains. MCCB composite scores were correlated with work, r=.51, p<.001, and everyday activities, r=. 35, p<.001. In contrast, in the 168 patients with MCCB composite scores of > 40, there was no correlation with social, everyday activities, or work outcomes, all r<.15, all p>.09. In patients with MCCB scores <40, both work and everyday activities were correlated with performance, both r> .21, both p<.005.
Conclusions: Even minimal symptoms may be a target for clinical attention in the domains of negative symptom but that less severe cognitive deficits may not correlate with functional outcomes.
Supported By: NIMH 63116; 78775; 93432
Keywords: Schizophrenia, Cognition, Negative Symptoms, Outcome, Prediction

T252. Olfactory Tasks in Affective and Non Affective Disorders

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Background: Objective: Impairments in olfaction have been documented in schizophrenia populations. However, it remains unclear how patients with schizophrenia (SZ) differ from patients with affective disorders in several olfactory tasks.
Methods: Odor discrimination, threshold and memory and identification tasks were performed in 22 controls, 44 bipolar and 30 schizophrenia patients using flow-dilution olfactometer and the 40-item University of Pennsylvania Smell Identification Test (UPSIT). In the olfactometry, n-butanol was used for odor threshold task. Sociodemographic, cognitive and psychopathological measures of were also ascertained from all participants.
Results: Significant differences between groups were observed only for odor identification and odor threshold tasks. The mean (± SD) UPSIT scores for odor identification, comparing SZ to healthy controls (HC) were 33.5 (5.8) vs. 28.3 (6.0), respectively ($P < 0.001$). Corresponding scores for SZ vs. HC on odor threshold tasks were 6.4 (1.5) vs. 3.9 (2.8), respectively ($P < 0.001$). These differences in odor identification and threshold remained significant ($P < 0.01$) after adjusting for age, sex and educational attainment in linear regression analyses. No differences were observed comparing bipolar patients to healthy controls in any of these tasks.
Conclusions: This study confirms research evidence of impaired odor perception and high order processing in SZ, and demonstrates that these differences were not generalized to bipolar affective disorder. Future studies should aim to uncover the pathophysiologic mechanisms of these findings.
Supported By: NIH/NIMH R01 award to Dr. Nwulia
Keywords: Schizophrenia, Bipolar Disorder, Odor Processing, Olfaction

T253. A Machine Learning Approach to Predict the Changes of Brain Functional Connectivity in Autism Spectrum Disorder From the Gene Expression Data

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Background: Understanding the biological mechanism of how gene expression affects functional connectivity is a challenge, especially for psychiatric disorders such as Autism Spectrum Disorder (ASD). In an effort to overcome this challenge, we developed a novel machine learning approach to identify gene expression changes that predict functional connectivity changes across brain regions.
Methods: Gene expression data for Frontal, Temporal and Occipital Cortex from ASD patients (N=33) and controls (N=34) were used to identify the differentially expressed genes in ASD (p<0.005) for every region. Enriched pathways and functions were calculated for ASD gene clusters obtained by K-Means. The resting-state fMRI data capturing the functional connectivity between these regions were obtained for Controls (N=77) and ASD patients (N=77). We used KS tests to quantify the significance of connectivity changes in ASD for each region (p<0.005). A support vector machine (SVM) model classified ASD functional connectivity changes across regions with ASD gene expressions (80/20% for training/testing).
Results: We identified 59, 6 and 1 shared ASD genes between Frontal-Temporal, Frontal-Occipital, and Temporal-Occipital cortexes, respectively. Enrichment analysis found neural

related functions such as axon and neuron cell components and synapsis pathways. The SVM model further classified ASD functional connectivity changes across different regions using ASD genes; the accuracy was 66.7% for Frontal-Temporal, 63.6% for Frontal-Occipital, 70% for Temporal-Occipital cortexes.
Conclusions: This work is an initial effort to identify gene expression biomarkers to predict functional connectivity changes in ASD, and can be extended to a machine learning platform for other psychiatric disorders.
Keywords: Gene Expression, Functional Connectivity, Autism Spectrum Disorder, Machine Learning, Support Vector Machine

T254. Human Neuronal-Like Cells Transdifferentiated From Blood Circulating Monocytes Express Glutamic Acid Decarboxylase (GAD)

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Background: Glutamic acid decarboxylase (GAD) is an enzyme critical for the synthesis of the inhibitory neurotransmitter GABA. This enzyme is associated in the pathophysiology of schizophrenia and bipolar disorder as it has been extensively studied in postmortem tissue. Less is known however, about the pathological role of GAD in live neuronal cells that come directly from patients.
Methods: We have developed a protocol to transdifferentiate blood circulating monocytes into neuronal-like cells in only 20 days. Unlike other models such as Induced Pluripotent Stem cells (IPSCs), the cell's genome is not altered with viral insertion which can become a confounder in illnesses with a strong but still misunderstood genetic component such as schizophrenia and bipolar disorder.
Results: We have transdifferentiated monocytes into neuronal-like cells from over 50 individuals and established that transdifferentiated neuronal-like cells resemble human neurons early in development, express several neuronal markers and conduct electrical activity. We have also determined that when these neuronal-like cells are exposed to either dopamine or colchicine, they respond similarly to neurons by retracting their neuronal arborizations. Moreover, transdifferentiation of monocytes deliver reproducible results in serial samples from the same individuals. In addition, we recently established via different laboratory techniques that Monocyte-Derived-Neuronal-like cells (MDNCs) express GAD.
Conclusions: Monocytes can be consistently transdifferentiated into neuronal-like cells. Since MDNCs can be obtained relatively rapid, larger cohorts of patients can be studied. Moreover, MDNCs express numerous neuronal genes and proteins including GAD. Therefore, this model opens the opportunity to study GAD directly in live neuronal-like cells from patients.
Keywords: Stem Cell, GABA, Neurodevelopment, Schizophrenia, Bipolar Disorder

T255. Cariprazine Enhances Monoaminergic Activity in the Hippocampus and Ventral Striatum of Rats: A Possible Basis for its Antipsychotic Effect

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Background: Cariprazine is an oral dopamine D3-preferring D3/D2 receptor partial agonist that also displays partial agonism at serotonin 5-HT1A receptors and antagonism at 5-HT2A and 5-HT2B receptors. This study aimed to characterize the effects of cariprazine on neurotransmitter efflux in the rat brain.
Methods: In vivo microdialysis was performed in awake, freely-moving rats after administration of cariprazine (0.03-0.3 mg/kg, p.o.), (+)-PD-128907 (D3 receptor agonist; 0.3 mg/kg, i.p.), and/or SB-277011A (D¬3 receptor antagonist; 10 mg/kg, i.p.). Extracellular levels of acetylcholine, dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), norepinephrine, and serotonin and its metabolite 5-hydroxyindole-acetic acid (5-HIAA) in the nucleus accumbens (NAc) and ventral hippocampus (HIP) were measured by UPLC-MS/MS.
Results: Cariprazine (0.1 or 0.3 mg/kg) increased dopamine, serotonin, and norepinephrine efflux in NAc ($P<.05$ for all), and dopamine, DOPAC, HVA, serotonin, and norepinephrine efflux in HIP ($P<.05$ for all). SB-277011A increased dopamine, DOPAC, HVA, norepinephrine, and 5-HIAA extracellular levels in both regions ($P<.05$ for all), and acetylcholine efflux in HIP ($P<.01$). The effects of SB-277011A and cariprazine (0.1 mg/kg) on dopamine and norepinephrine efflux were fully or partially blocked by (+)-PD-129807 ($P<.05$ for all).
Conclusions: These results suggest that the D3 receptor mechanism of cariprazine may contribute to increasing dopamine, serotonin, and norepinephrine efflux in NAc and HIP regions of the rat brain. Enhanced transmission of these neurotransmitters may contribute to the efficacy of cariprazine, including the procognitive, prosocial, and antipsychotic-like actions in animal models.
Supported By: Allergan
Keywords: Cariprazine, Dopamine, Schizophrenia, Microdialysis

T256. Differential Effects of Antipsychotics on Neuroinflammation and Energy Sensing in a Hypothalamic Cell Line

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Background: Antipsychotics are the cornerstone of treatment for schizophrenia but cause serious metabolic side-

effects. The hypothalamus is the primary brain region responsible for whole body energy regulation, and disruptions in hypothalamic energy sensing and inflammation are implicated in insulin resistance and obesity. Thus, hypothalamic inflammation and disturbed energy sensing could be involved in antipsychotic-induced metabolic disturbances, yet direct effects of antipsychotics on the hypothalamus has yet to be examined.
Methods: The immortalized rat hypothalamic cell line, rHypoE-19, was treated with olanzapine, clozapine or aripiprazole. Western blotting was used to measure the energy sensing protein AMPK, components of the insulin signaling pathway (AKT, GSK3B), and components of the MAPK pathway (ERK1/2, JNK, p38), the latter linked to inflammation. qRT-PCR was performed to determine changes in the mRNA expression of IL-6, IL-10, and BDNF.
Results: Olanzapine and clozapine increased pERK1/2 and pJNK, while aripiprazole only increased pJNK. Clozapine and aripiprazole increased pAMPK and inhibited insulin-induced pAKT. Olanzapine increased IL-6 while aripiprazole decreased IL-10. Olanzapine and aripiprazole increased BDNF expression.
Conclusions: Upregulation of pJNK alongside olanzapine-associated increases in IL-6, and aripiprazole-associated decreases in IL-10, suggests upregulation of pro-inflammatory pathways. Aripiprazole and clozapine inhibited insulin-stimulated pAKT and increased pAMPK, suggesting impaired hypothalamic insulin action by some, but not all, antipsychotics. Conversely, olanzapine and aripiprazole increased BDNF, a factor linked to the etiology of schizophrenia, suggesting BDNF upregulation as a mechanism of therapeutic action. Overall, our findings suggest differential effects of antipsychotics on hypothalamic neuroinflammation and energy sensing, and warrants further exploration into the mechanism of these effects.
Keywords: Atypical Antipsychotics, Hypothalamus, Neuroinflammation, Central Insulin

T257. The Phosphodiesterase 2A Inhibitor TAK-915 Ameliorates Cognitive Impairments and Social Withdrawal in N-Methyl-D-Aspartate Receptor Antagonist-Induced Rat Models of Schizophrenia

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Background: Modulation of the glutamatergic signaling pathway, including N-methyl-D-aspartate receptors (NMDAR), can provide a new therapeutic target for schizophrenia. Phosphodiesterase 2A (PDE2A) is highly expressed in the forebrain, and is a dual substrate enzyme that hydrolyzes both cAMP and cGMP, which play pivotal roles as intracellular second messengers downstream of NMDAR. Here we characterize the in vivo pharmacological profile of a selective and brain penetrant PDE2A inhibitor, TAK-915 as a novel treatment for schizophrenia.
Methods: Cyclic nucleotide contents and their downstream signaling in the rat brain were measured to confirm whether TAK-915 acts as a PDE2A inhibitor in vivo. Using several behavior tests, we investigated the potential of TAK-915 on cognition and social withdrawal in NMDAR antagonist-induced rat models of schizophrenia
Results: Oral administration of TAK-915 at 3 and 10 mg/kg significantly increased cGMP levels in the frontal cortex, hippocampus, and striatum of rats. TAK-915 at 10 mg/kg significantly upregulated the phosphorylation of a-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid receptor subunit GluR1 in the rat hippocampus. TAK-915 at 3 and 10 mg/kg significantly reversed episodic memory deficits induced by the NMDAR antagonist MK-801 in the rat passive avoidance test. TAK-915 at 10 mg/kg significantly attenuated working memory deficits induced by MK-801 in the rat radial arm maze test. Additionally, TAK-915 at 10 mg/kg reversed subchronic phencyclidine-induced social withdrawal in social interaction in rats. In contrast, TAK-915 did not produce antipsychotic-like activity.
Conclusions: TAK-915 has a potential to ameliorate cognitive deficits and social withdrawal in schizophrenia via upregulation of cyclic nucleotides in the brain.
Keywords: PDE2, Cognition, Schizophrenia

T258. Increased Thalamo-Temporal Connectivity Following Targeted Cognitive Training in Schizophrenia

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Background: Schizophrenia patients exhibit disruptions in thalamocortical connectivity that corresponds to both psychiatric symptoms and cognitive dysfunction. Targeted cognitive training (TCT) of the auditory system has been found to improve cognition in schizophrenia, but its influence on thalamocortical connectivity remains unknown. Using a region of interest (ROI) approach, the current study sought to identify thalamocortical connections that may be neuroplastic in response to TCT.
Methods: Schizophrenia patients were randomized to undergo 40 hours of TCT (N=22) or computer games (CG; N=22). Before and after training, individuals underwent resting state fMRI and cognitive testing. Thalamocortical connectivity was measured in 8 ROIs identified from a related study demonstrating differences between schizophrenia and healthy controls (2 HC>SZ ROIs and 6 SZ>HC ROIs). Group x time changes were assessed, as well as correlations with cognition change.
Results: Two SZ>HC ROIs showed significant group x time interactions: thalamic connectivity with the left superior temporal cortex (F=7.50;p=.008) and right superior temporal cortex (F=4.56;p=.036) characterized by connectivity increases in the TCT condition. Change in connectivity and change in global cognition showed between

groups slope differences in the left (t=2.92;p=.006) and right temporal cortex (t=2.55;p=.01). Increases in left thalamus-temporal connectivity correlated with increases in cognition in TCT (r=.50;p=.02); Right thalamus-temporal connectivity showed a relationship in the same direction (r=.28;p>.05).
Conclusions: The TCT group showed increased thalamo-temporal connectivity that coincided with improved cognition. This suggests that auditory training influences intrinsic functional connectivity in a compensatory manner, such that hyperconnectivity between the thalamus and auditory cortex increases in coherence and corresponds to improved cognition.
Supported By: NIMH R01
Keywords: Thalamocortical Connectivity, Cognitive Training, Recent-Onset Schizophrenia, Auditory Cortex

T259. Effects of Adverse Childhood Experiences on Alcohol- and Stress-Related Phenotypes in Dependent and Non-Dependent Drinkers

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Background: Adverse childhood experiences (ACEs) are associated with alcohol use disorder and posttraumatic stress disorder (PTSD). Our objective was to examine the influence of ACEs in treatment-seeking alcoholic-dependent inpatients with and without PTSD, and in a separate sample to evaluate the effects of ACEs on drinking history and IV alcohol self-administration in non-dependent drinkers.
Methods: Inpatients (N=455) with and without PTSD were assessed for childhood trauma using the Childhood Trauma Questionnaire (CTQ). A subset (N=115) was analyzed for brain volume differences. A separate non-dependent sample (N=472) was also administered the CTQ and Timeline Follow Back (TLFB) to assess recent drinking history. A subset (N=136) underwent an IV alcohol self-administration session.
Results: CTQ-positive inpatients started drinking at an earlier age and had greater alcohol dependence severity, neuroticism, anxiety symptoms, and aggression (all p's<0.01) compared to those without childhood trauma. Subjects with PTSD, on average, had higher levels of neuroticism, anxiety and aggression, with these effects occurring additively with childhood trauma (all p's<0.02). There were brain volume differences between CTQ-positive and CTQ-negative inpatients among the key subcortical reward and limbic structures when controlled for age and sex. In the non-dependent sample, CTQ-positive individuals had heavier drinking histories and greater self-administration during the session (all p's<0.01).
Conclusions: These findings indicate that childhood trauma results in a more severely affected phenotype among alcohol-dependent patients and in greater alcohol consumption among non-dependent drinkers. Future directions include investigations of personality factors and genetic influences that may be associated with AUD and PTSD, and the influence of childhood trauma exposure.
Supported By: Supported by the NIAAA Division of Intramural Clinical and Biological Research (ZIAAA000466).
Keywords: Childhood Trauma, PTSD - Posttraumatic Stress Disorder, Self-administration, Brain Volumes, Alcohol

T260. Oxytocin-Enhanced Motivational Interviewing Group Therapy for Methamphetamine Use Disorder in Men Who Have Sex With Men: Preliminary Results From a Randomized Controlled Trial

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Background: Despite significant morbidity, no FDA-approved psychopharmacological treatments exist for methamphetamine use disorder (MUD). Methamphetamine-related problems with social perception and stress regulation contribute to excessive attrition rates, which limit the validity of MUD treatment research and effectiveness of psychosocial treatments. In animal models of MUD, oxytocin administration has produced encouraging results. Oxytocin is a hypothalamic neuropeptide with prominent roles in social attachment and autonomic control in response to stress. This is the first trial investigating oxytocin administration in humans with MUD. Outcomes include methamphetamine use, treatment retention, and stress reactivity.
Methods: Twenty-seven individuals with MUD received oxytocin 40-IU or placebo intranasally prior to each of six, weekly, 90-minute motivational interviewing group therapy (MIGT) sessions in this randomized, double-blind study. Weekly urine toxicology results and attendance were recorded. High frequency heart rate variability (HF-HRV), an indicator of parasympathetic control, was derived from electrocardiogram recorded throughout each MIGT session.
Results: Our generalized estimating equations models showed a significant main effect of drug on methamphetamine use such that oxytocin groups had fewer meth-positive urines [B=2.06, SE=0.86, p=0.017], and a trend-level main effect of drug on attendance such that oxytocin groups had fewer absences [B=-4.57, SE=2.50, p=0.068], than placebo groups. Moreover, our preliminary analysis demonstrated a significantly higher overall HF-HRV among the groups receiving oxytocin, Mean(SEM): OT: 5.21(0.53), PL: 3.22(0.62), t(12.26)=2.28, p=0.041.
Conclusions: This novel translational protocol bridges ample animal data and much-needed, innovative, clinical treatments for difficult-to-treat individuals with MUD.

Promising preliminary results from our modest sample show improvements in methamphetamine use, retention, and stress regulation.
Supported By: University of California, San Francisco Resource Allocation Program
Keywords: Oxytocin, Methamphetamine Addiction, Psychophysiology, Translational Research, Novel Intervention

T261. Working Memory Training in Alcohol Use Disorder: A Randomized Controlled Trial

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Background: Alcohol use disorder (AUD) is associated with cognitive deficits such as impaired executive functions, hypothesized to contribute to the progression of the disease and worsen treatment outcome. Training of working memory (WM) to improve cognitive functions and in turn the alcohol use outcomes have been proposed as a novel treatment strategy.
Methods: AUD patients recruited to an outpatient addiction clinic were randomized to receive 5 weeks of active WM training (n=25) or control training (n=25). Primary outcomes were WM function and change in self-reported heavy drinking. Secondary outcomes were craving, other drinking outcomes and performance on a range of neuropsychological tasks of executive functions.
Results: The active training group compared to controls demonstrated a significantly greater improvement in verbal WM ($F(1,48)=5.01$;$p=0.029$) but not spatial WM ($F(1,46)=0.017$;$p=0.896$). No statistically significant effect of training was found on the primary drinking outcome ($F(1,47)=1.602$;$p=0.212$), but a trend was observed indicating that WM training reduces number of drinks per drinking occasion ($F(1,47)=3.471$;$p=0.069$). WM training had no effect on craving or any of the other neuropsychological tasks (all $p>0.05$).
Conclusions: Cognitive training can improve WM function in individuals with AUD, suggesting that such labour-intensive interventions are feasible in this patient population. The results are inconclusive regarding WM training effect on drinking and transfer effects to other cognitive domains. Future studies should evaluate WM training in larger sample sizes, possibly as an adjunct to evidence based treatments for AUD to assess potential synergistic effects.
Supported By: The Söderström König Foundation. Systembolaget.
Keywords: Alcohol Use Disorder, Working Memory, Cognitive Training

T262. Working Memory Moderates Relations Between Alcohol Demand Characteristics, PTSD Arousal Symptoms and Alcohol Use

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[1]San Francisco Veterans Affairs Medical Center, [2]San Francisco Veterans Affairs Health Care System; University of California, San Francisco, [3]San Francisco Veterans Affairs Health Care System

Background: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are highly comorbid with complex and often unclear associations. Working memory (WM) dysfunction may represent a shared mechanism implicated in emotion regulation and control over impulsive alcohol use. Here, we investigate the extent to which WM and a laboratory-based behavioral economic task influence effects of PTSD symptoms on real-world alcohol consumption.
Methods: 88 Veterans completed an Alcohol Purchase Task (APT) and were assessed for PTSD (PCL-IV), alcohol use (Timeline Followback; average drinks per week in past 90 days), and WM (WAIS-III). We conducted a series of moderated mediation models (Hayes Process Model 58) to examine the effects of each PTSD symptom cluster on alcohol use, controlling for premorbid verbal IQ (Wechsler Test of Adult Reading) and age. APT "Pmax" (i.e., price at which demand becomes elastic) was entered as the mediator and WM as the moderator in each model.
Results: The direct effect of PCL arousal on alcohol use was significant ($B=0.04$, $p=0.04$). While Pmax did not mediate the relationship between arousal and alcohol use, WM moderated relations between arousal and Pmax (WM*arousal: $B=-0.02$, $p=0.02$) and between Pmax and real-world alcohol use (WM*Pmax: $B=-0.07$, $p=0.05$).
Conclusions: We find that for poor WM subjects, PTSD symptoms were linked to greater over-valuing of alcohol in a laboratory setting, whereas for high WM subjects, alcohol demand characteristics predicted less real-world alcohol use. This work highlights WM as a potential target for interventions geared towards reducing alcohol use in Veterans with co-occurring PTSD/AUD.
Supported By: Department of Defense/CDMRP PH TBI, W81XWH-12-2-0137 (Batki); Department of Defense/Gallo Clinic & Research Center at UCSF W81XWH-11-2-0245 (Batki)
Keywords: Alcohol Use Disorder, PTSD - Posttraumatic Stress Disorder, Working Memory, Behavioral Economics, Clinical Trial

T263. Psilocybin Improves Cognitive Control and Downregulates Parietal Cortex in Treatment-Seeking Smokers

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[1]IRP, NIDA, NIH, [2]Johns Hopkins University, BPRU

Background: Prior data suggests the 5-HT2A receptor agonist psilocybin (PSILO) improves smoking cessation outcomes. Here, we examine cognitive and neurobiological

mechanisms underlying these encouraging results. The multi-source interference task (MSIT) is employed as an assay of changes in cognitive control processes mediated by PSILO administration in treatment-seeking smokers.
Methods: N=9 treatment-seeking smokers performed the MSIT while undergoing fMRI scanning during 2 sessions: prior to beginning cessation treatment and again 24 hours after receiving a single PSILO dose (30mg/70kg) in a supported, therapeutic context. Behavioral and fMRI data were collected during each fMRI session.
Results: Following PSILO administration as compared to baseline, a reduction in congruency effect (incompatible − compatible) for correct trial reaction time (t(8)= 6.21, p=.003) was observed. However, no difference in congruency effect for accuracy (t(8)=0.52, p=.61) was observed. Concurrently, fMRI results showed a reduced congruency effect in MSIT-elicited activation in bilateral superior parietal cortex following PSILO (p- corrected <.05)[Right: TLRC, xyz, -27, -64, 39; Left: 27, -62, 46]). In addition, the positive correlation between reaction time and parietal activation congruency effects observed at baseline (r=.67, p=.047) was absent following PSILO (r=.25, p=.50).
Conclusions: The observed PSILO-mediated decrease in task-evoked brain activity is consistent with the limited literature on the acute effects of PSILO in healthy participants. The posterior parietal ROI identified has been previously labeled a multiple demand hub, showing activation with increased demand across several cognitive control tasks. The current results suggest that, for smokers, PSILO decreases the salience of conflict-inducing stimuli which paradoxically leads to improved performance.
Supported By: NIDA-IRP, Heffter Research Institute, Beckley Foundation
Keywords: Cognitive Control, Psilocybin, Cigarette Smoking, Superior Parietal Cortex

T264. Differential Effects of Left and Right Prefrontal High Frequency rTMS on Resting State fMRI in Healthy Individuals

Renee Schluter[1], Jochem Jansen[1], Ruth van Holst[1], Wim van den Brink[1], and Anna Goudriaan[1]

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Background: High frequency repetitive transcranial magnetic stimulation (HF-rTMS) has gained interest in treatment of psychiatric disorders such as depression and substance dependence. It is postulated that HF-rTMS accomplishes its effect by influencing neuronal networks. The dorsolateral prefrontal cortex (dlPFC) is frequently chosen as target for HF-rTMS. However, little is known about the differential effect of left and right dlPFC HF-rTMS on resting state functional connectivity networks in healthy individuals.
Methods: We assessed the differential effects of left and right HF-rTMS (corrected for sham) on Independent Component Analysis (ICA) defined functional connectivity networks in a sample of 45 healthy individuals. During the first scanning session baseline functional connectivity was assessed. During the second session, either left, right or sham dlPFC HF-rTMS (60 5 second trains of 10Hz at 110% motor threshold) was applied. ICAs were performed to assess baseline differences and stimulation effects on within and between network functional connectivity.
Results: A significantly different effect of left (M = -6.83, SD = 16.40) and right (M = 10.3, SD = 7.10) dlPFC stimulation was found in the within salience network connectivity (t(28) = 3.71, p < .001): right dlPFC stimulation led to increased functional connectivity, whereas left dlPFC stimulation led to decreased functional connectivity within the SN. No differences between left or right dlPFC stimulation were found in other within network connectivity or in between network connectivity.
Conclusions: These results suggest that left and right HF-rTMS may have different effects and more research is needed on the clinical consequences.
Supported By: NwO (VIDI grant number: 91713354); ERAB (EA 1027)
Keywords: Resting State Functional Connectivity, HF-rTMS, DLPFC

T265. Fluctuations in Craving and Mood State Bias Subjective Valuation in Addiction

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[1]New York University, [2]New York University School of Medicine

Background: How craving and mood states (e.g., stress, boredom) bias behavior toward rewarding but less adaptive alternatives and away from an individual's health goals is poorly understood, yet play a critical role in addiction and eating disorders. Here we test the hypothesis that underlying this bias is a state-dependent increase in the subjective value of these rewarding but less-adaptive choice alternatives.
Methods: 27 treatment-seeking opioid users completed a decision-making task that probed their momentary willingness-to-pay for a range of real opioid use−related and −unrelated goods, a quantitative measure of their value. These goods were identified as most (least) related to an individual subject's use. To capture how dynamics in spontaneous opioid craving and mood affect subjective valuation, patients completed the task over 2 days while continuously reporting their current opioid craving, stress level, boredom, and happiness. Skin conductance and facial EMG were measured concurrently as indices of arousal and valence, respectively.
Results: Subjects were willing to pay more specifically for personalized opioid-related goods when experiencing higher craving, stress, and boredom and lower happiness (subjective state level X opioid-relatedness: P<0.016). Despite mild correlation across subjective states (R=|0.14−0.51|), the effects of each on valuation were largely independent, particularly of craving and stress. Analysis of physiological data is ongoing, but we hypothesize these data will serve as

auxiliary, objective measures of how subjective states bias valuation.
Conclusions: These data suggest craving and stress both enhance the value of less-adaptive choice alternatives when these are immediately rewarding, potentially reflecting a compensatory mechanism aimed at buffering these states.
Supported By: NARSAD Young Investigator Award
Keywords: Craving, Stress, Decision-making, Subjective Value, Opioid Addiction

T266. Memory Deficits are Reversible With Sustained Cannabis Abstinence Among Cannabis Using Adolescents

Randi Schuster[1], **Maya Hareli**[1], Emily Nip[1], Jodi Gilman[1], David Schoenfeld[1], and A. Eden Evins[1]

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Background: Studies show neurocognitive dysfunction among adolescent cannabis users, yet it is unclear for what duration these deficits persist. Reversibility of neurocognitive dysfunction with abstinence would support a putative causal impact of cannabis on brain functioning.
Methods: Participants (N = 88) were randomized to four weeks of cannabis abstinence (MJ-Abst; n=62) or monitoring (MJ-Mon; n=26). The Cambridge Neuropsychological Test Automated Battery (CANTAB) assessed neurocognition at baseline, and weekly for four weeks.
Results: Biochemically-confirmed 30-day continuous abstinence was achieved by 53 (85.5%) of MJ-Abst participants. There was a main effect of time [$F(4,88)=13.80$, $p<0.0001$] on attention, but group and the group by time interaction were not significant [p-values>0.55]. There was a main effect of group on memory [$F(1,88)=10.75$, $p=0.002$], with abstinence associated with better memory overall [$\beta=0.22$, $t(88)=3.28$, $p=0.002$]. The main effect of time and the group by time interaction were not significant [p-values>0.77]. Only MJ-Abst exhibited an improvement in memory from baseline to week 1 [$\beta=0.26$, $t(88)=5.60$, $p<0.0001$]. There was no change in performance at all other time points across group [p-values >0.36]. MJ-Abst performed significantly better than MJ-Mon at week 1 [$\beta=0.26$, $t(88)=3.43$, $p=0.0009$], week 2 [$\beta=0.19$, $t(88)=2.25$, $p=0.03$], and week 3 [$\beta=0.25$, $t(88)=2.83$, $p = 0.006$]. The effect on memory was driven by an effect on verbal memory, specifically initial encoding.
Conclusions: Findings support an adverse but likely reversible effect of cannabis use among adolescents on memory, specifically the ability to learn new information, but not attention. Improvement in verbal learning appears to occur in the first week.
Supported By: 5K23DA042946-02
Keywords: Cannabis, Adolescence, Neurocognition, Learning and Memory, Attention

T267. Psychopathic Traits and Stimulus-Processing in Addiction: How Psychopathy and Addiction Interact to Influence Drug and Food Processing in the Brain

William Denomme[1], Matthew Shane[1], and Isabelle Simard[1]

[1]University of Ontario Institute of Technology

Background: Increasingly psychopathic substance-dependent subjects exhibited reduced neural reactivity to drug compared to neutral images (Cope et al., 2014). However, we presented the opposite relationship based on preliminary results at the Society of Scientific Study of Psychopathy conference when using food as a control stimulus (Denomme & Shane, 2017). The current study consisted of subsequent analyses to further understand this relationship.
Methods: Groups of n=47 cocaine-dependent and n=58 non-dependent subjects viewed cocaine and food videos in a fMRI scanner. We assessed the moderating effect of psychopathic traits on parameter estimates of peak-voxel BOLD signal changes in response to cocaine and food video conditions from the dorsomedial prefrontal cortex (DMPFC; MNI: -3, 45, 24), insula (MNI: 36, 0, -21), ventral striatum (MNI: 6, 12, -6), amygdala (MNI: -39, 0, -21), and anterior cingulate cortex (ACC; MNI: -6, 18, 21). These estimates were entered into between-groups ANOVA models. Partial correlations were computed between these estimates and psychopathic traits while controlling for age and drug use within each group.
Results: Dependent, compared to non-dependent participants, exhibited greater neural reactivity to cocaine relative to food videos in the amygdala ($F=4.76$, $p=.031$), insula ($F=4.67$, $p=.033$), and ACC ($F=11.04$, $p=.001$). Psychopathic traits were associated with DMPFC ($r=-.33$, $p=.026$) and amygdala ($r=-.30$, $p=.047$) deactivations in response to food videos among the dependent group.
Conclusions: The results of this study further demonstrate how psychopathic traits are implicated into drug and food processing abnormalities in addiction. They implicate further research into how the structural correlates of psychopathy explain these functional neural processing abnormalities.
Supported By: RO1DA026932
Keywords: Addiction, Psychopathy, BOLD fMRI, Craving, Reward

T268. Pavlovian-To-Instrumental Transfer and Outcome Devaluation in Human Alcohol Dependence

Tim van Timmeren[1], Stephanie L. Quail[2], Dirk E.M. Geurts[3], Bernard W. Balleine[2], Ruth J. van Holst[3], and Anna E. Goudriaan[1]

[1]Academic Medical Centre, University of Amsterdam, [2]Decision Neuroscience Lab, School of Psychology, [3]Donders Institute for Brain, Cognition and Behaviour, Radboud University

Background: In the last decade, addiction research has increasingly focused on the neural processes that mediate the acquisition and performance of goal-directed instrumental actions. Deficits in goal-directed control and impairments in habit learning processes have been described as ultimately resulting in compulsive drug seeking, one of the hallmarks of addiction. However, direct evidence for the

role of these processes has so far mainly come from animal studies.

Methods: In this study, we sought to establish whether there are general deficits in goal-directed and habitual action in patients with alcohol use disorder (AUD). To this end, we assessed (i) the influence of cues predicting food rewards on instrumental action in a Pavlovian-to-instrumental transfer (PIT) test and (ii) habitual behavior in an outcome devaluation test. Brain activity was measured during both tests using functional MRI in n=40 AUD's and n=23 matched healthy control individuals (HCs). Moreover, relapse was assessed after six months.

Results: We found (i) significant behavioral specific and general PIT effects for all participants, mediated by distinct corticostriatal BOLD signals, but no significant differences between AUD's and HCs; (ii) a significant behavioral devaluation effect for all participants, but no significant group differences. Contrary to previous findings, we did not find a relation with relapse and (neuronal) PIT effects.

Conclusions: This is the first study to investigate goal-directed learning in human AUD using specific and general PIT and a devaluation procedure. Our results do not indicate any deficits in integrating action-outcome associations in AUD's, nor any relation with later relapse.

Supported By: VIDI (NWO-ZonMw) [grant number 91713354]

Keywords: Alcohol Addiction, Goal-directed Learning, Pavlovian-Instrumental Transfer, Decision Making, Substance Use Disorder

T269. Value-Based Decision-Making of Cigarettes and Non-Drug Rewards in Dependent and Occasional Smokers: An fMRI Study

Will Lawn[1], Tom Freeman[1], Abdelmalek Benattayallah[2], James Bisby[1], Ludovico Mitchener[1], Val Curran[1], Chris Dodds[2], and Celia Morgan[2]

[1]University College London, [2]University of Exeter

Background: Value-based decision-making is theoretically impaired in substance use disorders. In dependent and occasional cigarette smokers, we aimed to: (1) identify the brain's value signal for cigarettes and vouchers, (2) investigate neural and behavioural decision-making group differences.

Methods: Smokers (20 dependent; 19 occasional) completed a decision-making task, in which cigarettes and vouchers could be purchased. In the first stage (pre-scanning), participants stated their willingness-to-pay (WTP) for a variety of cigarette 'bundles' (e.g. 5 cigarettes) and voucher 'bundles' (e.g. 5 vouchers). In the second stage (during scanning), participants made a series of purchase choices about the 'bundles'. Using an ROI approach, and parametric modulation, we investigated which brain regions encode value signals and examined group differences. We also investigated behavioural group differences in WTP and choices, and the relationships between them.

Results: Dependent smokers had a higher WTP for cigarettes than occasional smokers ($t37=4.262$, $p<0.001$). Choices were positively affected by WTP ($\beta=0.984$, $p<0.001$). Dependent smokers were more sensitive to changes in WTP for cigarettes than vouchers ($\beta=1.063$, $p<0.001$), while the opposite was true of occasional smokers ($\beta=-0.232$, $p=0.015$). In the ROI analyses, we identified a cigarette value signal within the vmPFC across both groups ($p(FWE)=0.022$, [x=0, y=53, z=-10]). Other effects were null.

Conclusions: Dependent smokers valued cigarettes more than occasional smokers and, when making choices, were more sensitive to the value of the cigarettes on offer. We identified a value signal for cigarettes in the vmPFC, for the first time. However, we did not observe any group differences in neural processing of value between groups.

Keywords: Addiction, Cigarette Smoking, Decision Making, Functional MRI, Reward

T270. The Role of Emotional Context in Prepotent Response Inhibition: An fMRI Investigation

Aleksandra Herman[1], David Watson[2], Hugo Critchley[2], and Theodora Duka[1]

[1]University of Sussex, [2]Brighton and Sussex Medical School

Background: Impulsivity is considered a crucial factor in substance misuse; therefore, it is essential to understand modulators of impulsive behaviour. This study investigated how emotional task-independent context affects performance on the motor impulsivity task in binge drinking (BD) and underlying neural mechanisms.

Methods: Thirty healthy volunteers completed an Affective Stop Signal Task (ASST) in the functional magnetic resonance imaging (fMRI) scanner. ASST assessed the ability to inhibit a prepotent motor response in the task-independent emotional (fearful faces) and neutral (neutral faces) contexts.

Results: Emotional context did not affect participants' ability to inhibit a prepotent motor response, $t(29) = .62$, $p = .537$. However, the difference in response inhibition measure in the Fearful vs Neutral conditions negatively correlated with the binge score, $r(30) = -.376$, $p = .041$, indicating that increased BD was associated with better performance in the Fearful relative to Neutral context.

At the neural level, BD score was associated with increased activity in the right frontal pole during successful execution of the inhibitory action (Stop Success>Go Correct). Moreover, BD was related to decreased activity in regions associated with visuospatial attention and motor response (superior parietal lobule, precentral gyrus, supplementary motor area) during successful stopping in the Fearful relative to Neutral context.

Conclusions: Binge drinkers need to engage more neural resources to successfully inhibit a prepotent motor response. However, this effect is attenuated in the emotional context: Individuals with higher BD score showed better performance and decreased activity in visuospatial brain areas in the Fearful vs Neutral context.

Supported By: Sussex Neuroscience

Keywords: Impulsivity, Emotion, Functional MRI, Binge Drinking, Alcohol

T271. Cannabidiol Reverses Attentional Bias to Cigarette Cues in a Human Experimental Model of Tobacco Withdrawal

Chandni Hindocha[1], Tom Freeman[1], Meryem Grabski[2], Jack Stroud[1], Holly Crudgington[1], Alan Davies[1], Ravi Das[1], Will Lawn[1], Celia Morgan[3], and Val Curran[1]

[1]University College London, [2]University of Bristol, [3]University of Exeter

Background: Current pharmacological treatments for smoking cessation have limited efficacy and can produce significant side effects. Cannabidiol (CBD), a non-intoxicating cannabinoid in cannabis, may be a promising novel smoking cessation pharmacotherapy with anxiolytic properties and minimal side effects.
Methods: Randomized, double-blind laboratory crossover study utilising an experimental medicine approach to investigate whether CBD would reduce withdrawal, the salience of drug cues and response inhibition (go/no-go) following overnight abstinence in thirty dependent (non-treatment seeking) cigarette smokers. Participants attended a satiated session, followed by two overnight abstinent sessions (compliance verified) where they received either 800mg oral CBD or placebo (PBO) in a counterbalanced order. Withdrawal, craving, side effects, heart rate and blood pressure were assessed repeatedly.
Results: When participants received placebo, tobacco abstinence increased automatic attentional bias compared to satiety ($p=.001$, $d=.789$). However, CBD reversed this effect, such that automatic attentional bias was directed away from cigarette cues ($p=.007$, $d=.704$) and no longer differed from satiety ($p=.82$). Abstinence, compared to satiated, increased commission errors on the go/no-go. CBD, compared to placebo, increased commission errors ($p=0.038$). Craving and withdrawal were greater in abstinence compared with satiety, but unaffected by CBD. No side effects of CBD emerged and systolic blood pressure decreased under CBD during abstinence.
Conclusions: In the first study to investigate CBD for nicotine withdrawal, our results suggest CBD may exert its effects on addiction via a reduction in the salience of drug cues and this may be a key neurocognitive mechanism through which CBD may help treat tobacco use disorders.
Supported By: MRC
Keywords: Abstinence, Tobacco Use Disorder, Cannabinoids, Salience, Experimental Medicine

T272. Association Between LINE-1 Methylation Patterns and Cigarette Smoking in Individuals With Methamphetamine Use

Rasmon Kalayasiri[1], Korakot Kraijak[1], and Apiwat Mutirangura[1]

[1]Chulalongkorn University

Background: Alteration of gene expression is caused by the use of psychoactive substances such as cigarettes and methamphetamine (MA), that may be caused by changes in DNA methylation. The aim of the study was to compare patterns of DNA methylation, a type of epigenetic alteraction that occurs when cytosine bases were methylated, between individuals with and without cigarette initiation (CI) in heavy and non-heavy MA users.
Methods: Patterns of DNA methylation in perpheral blood of 331 heavy and non-heavy MA (cut-point, ~1,000 episodes of MA use in lifetime) users with and without cigarette initiation (cut-point, ~100 cigarettes in lifetime) at a Thai substance abuse treatment center was measured by using the technique combined bisulphite restriction analysis long interspersed nuclear element 1s (COBRALINE-1s). Demographic and substance use variables were obtained from the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). Non-heavy MA users (non-MA) without cigarette initiation (non-CI) were used as a matching-control group.
Results: Individuals with heavy MA use and CI had lower level of DNA methylation of LINE-1s than the control group. Amount and frequency of cigarette smoking did not associate with level of DNA methylation. In contrast, long duration of MA use in the heavy users promoted the increase of hypomethylation. However, recent number of episodes of MA use did not associate with patterns of LINE-1s methylation.
Conclusions: Effects of CI and MA on LINE-1s methylation occurs independently with substance use variables including lifetime frequency/amount of cigarette smoking and recent MA use, respectively.
Supported By: Nation Science and Technology Development Agency (NSTDA) of Thailand
Keywords: Cigarette Smoking, Methamphetamine, LINE-1s, DNA Methylation, Epigenetics

T273. A Critical Role for the Globus Pallidus in Cocaine-Triggered Plasticity Revealed Byrabies Activity Screen

Kevin Beier[1], Christina Kim[1], Paul Hoerbelt[1], Lin Wai Hung[1], Boris Heifets[1], Kathy DeLoach[1], Tim Mosca[2], Sophie Neuner[1], Karl Deisseroth[1], Liqun Luo[1], and Robert Malenka[1]

[1]Stanford University, [2]Thomas Jefferson University

Background: Identification of neural circuit changes contributing to behavioral plasticity has routinely been conducted on candidates that were pre-selected based on past results.
Methods: Here we present an unbiased method for identifying experience-triggered circuit-level changes in neuronal ensembles. Using rabies virus monosynaptic tracing we mapped cocaine-induced global input changes onto ventral tegmental area (VTA) neurons
Results: Cocaine increased rabies labeled inputs from the globus pallidus externus (GPe), a basal ganglia nucleus that was not known to participate in behavioral plasticity triggered by drugs of abuse. This change was induced by a variety of abused substances with different pharmacological mechanisms, but was not observed with the psychoactive but non-addictive substance fluoxetine. We then investigated the

source of this increase, assaying for potential changes in synapse number, strength, or activity of input populations. Using fiber photometry in awake, behaving animals, we demonstrate that cocaine increases the spontaneous activity of GPe parvalbumin neurons, and show using slice electrophysiology that the intrinsic excitability of these neurons is chronically enhanced after a single exposure to cocaine. Furthermore, we demonstrate that targeted activity manipulations can modulate the extent of rabies labeling. In addition, inhibition of GPe activity revealed its vital role in two different forms of cocaine-triggered behavioral plasticity, locomotor sensitization and conditioned place preference. This behavioral inhibition was facilitated, at least in part, by GPe-mediated local disinhibition of VTA dopamine neuron activity.
Conclusions: These results suggest that rabies-based unbiased screening of changes in input populations can identify previously unappreciated circuit elements that critically support behavioral adaptations.
Supported By: SOBP travel award
Keywords: Dopamine, Cocaine, Ventral Tegmental Area, Basal Ganglia, Methods

T274. EEG Asymmetry During Emotional Challenge Predicts Future Depressive Symptoms

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Background: Research supports electroencephalographic (EEG) asymmetry as a promising biomarker of risk for depression. Greater depressive symptoms are linked to greater right than left prefrontal cortex (PFC) activity, a relationship that is more robust when EEG is recorded during emotional challenge as opposed to a resting state. Although PFC asymmetry recorded at rest also predicts future depressive symptoms in never-depressed individuals, bolstering its potential role as a biomarker of depression, research has yet to demonstrate this relationship in EEG recorded during emotional challenge.
Methods: At baseline, Current-source-density (CSD) transformed EEG was recorded while 54 healthy control participants experienced a directed facial action (DFA) task, wherein they were instructed to move facial muscles into configurations reflecting joy, anger, sadness, and fear. Participants completed the Beck Depression Inventory—II (BDI-II) at baseline and one year following the EEG recording, the latter reflecting their worst month during the past year. A linear-mixed model was computed for alpha-band (8-12 Hz) PFC asymmetry score as the dependent variable, with DFA condition (approach: joy, anger; withdrawal: sadness, fear), channel (F2F1, F4F3, F6F5, F8F7), and BDI-II at follow-up (with and without accounting for baseline BDI-II) as independent variables.
Results: A main effect of follow-up BDI-II score demonstrated that baseline right PFC asymmetry was associated with higher BDI-II at follow-up, regardless of whether BDI-II baseline variance had first been removed ($p<.01$).
Conclusions: The present study extends previous research indicating that CSD-referenced EEG asymmetry measured during emotional challenge may be a biomarker for first onset depression or depressive symptom increase in healthy adults.
Supported By: National Institutes of Health (NIH)
Keywords: Electroencephalography (EEG), Frontal Alpha Asymmetry, Biomarkers, Depression

T275. Going Wireless: Validation of a Novel Neurostimulation Technology in a Conditioned Place Preference Task

Lisa Maeng[1], Maria Murillo[2], Meng-Chen Lo[1], Daniel Freeman[3], Mohammed Milad[4], and Alik Widge[1]

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Background: Deep brain stimulation (DBS) technologies have attracted increasing interest in the treatment of psychiatric disease due to growing evidence of disrupted brain circuits and connectivity in several psychopathologies. Animal models of DBS would be helpful, but to mimic human DBS, those stimulators should not require bulky, limiting tethers. We aimed to validate a novel wireless neurostimulator device, the e-Particle (EP), using rewarding medial forebrain bundle (MFB) stimulation in a conditioned place preference (CPP) paradigm.
Methods: Adult male rats were implanted with a commercial tethered electrode into the MFB in one hemisphere and the EP in the contralateral hemisphere, for within-subject comparisons of stimulation. All animals were tested for CPP in an open field for baseline, stimulation, and test sessions. EP stimulations were administered via a wireless transmitter, whereas the wired electrode was stimulated through a tethered isolator.
Results: A repeated measures ANOVA revealed no difference between the wired and wireless stimulation types [$F(2,87)=2.41$, $p>0.05$]. The amount of time spent in the stimulation quadrant increased from baseline during stimulation [wired: 15.6%, $t(47)=-3.29$, $p<0.01$; wireless EP: 11.8%, $t(41)=-2.26$, $p<0.05$], as well as during the test session [wired: 21.5%, $t(47)=-4.20$, $p<0.01$; wireless EP: 15.6%, $t(41)=-2.64$, $p<0.05$] when stimulation was absent. Postmortem c-fos staining showed activation in MFB-innervated cortex from both wired and wireless stimulation.
Conclusions: Wireless EP stimulation can shape behavior comparably to traditional wired stimulation, although the range of stimulation parameters is limited by the EP's design. Future studies should further assess the efficacy of EP neurostimulation in other behavioral assays or neurologic disease models.
Supported By: Draper Laboratory, The Brain and Behavior Research Foundation, Harvard Brain Science Initiative Bipolar Seed Grant Program
Keywords: Electrophysiology, Neurostimulation, Deep Brain Stimulation, Medial Forebrain Bundle, Conditioned Place Preference

Friday, May 11, 2018

POSTER SESSION 2
5:00 p.m. - 7:00 p.m.

F1. The Effect of Treatment Type on Improvement of Subjective Sleep Quality in Complicated Grief

Allison Young[1], Kristin Szuhany[1], Julia Spandorfer[1], Susanne Hoeppner[2], Meng Li[1], Edward Pace-Schott[2], Christine Mauro[3], Sidney Zisook[4], Charles Reynolds[5], Katherine Shear[3], and Naomi Simon[6]

[1]NYU School of Medicine, [2]Massachusetts General Hospital & Harvard Medical School, [3]Columbia University, [4]University of California San Diego and San Diego Healthcare System, [5]University of Pittsburgh School of Medicine, [6]Massachusetts General Hospital & Harvard Medical School & NYU Langone Medical Center

Background: Self-reported sleep impairment has been reported in complicated grief (CG), and is correlated with CG severity. We examined the effect of treatment on sleep quality in CG.
Methods: 395 adults with CG were randomized to 20 weeks of Complicated Grief Therapy (CGT) + placebo, CGT + citalopram, citalopram, or placebo. This analysis compared change in four Quick Inventory of Depressive Symptoms (QIDS-SR) sleep items (1. falling asleep, 2. sleep during the night, 3. waking up too early, 4. sleeping too much) and a grief anchored Pittsburgh Sleep Quality Index summary item (PSQI-TS: Trouble sleeping) by treatment group.
Results: At baseline, 91.3% of participants had scores $\geq$2 on at least one QIDS item and PSQI-TS mean$\pm$SD of 2.0$\pm$1.1. Change scores (Week 0 to 20, LOCF) were analyzed with ANCOVA controlling for baseline. Two of the five sleep measures, the PSQI-TS and QIDS item 2, significantly improved with treatment. Sleep improved significantly more in the therapy than non-therapy groups for the PSQI-TS (CGT: Baseline 2.0$\pm$1.1 to Endpoint 0.8$\pm$1.1 vs. No CGT BL 1.9$\pm$1.1 to EP 1.2$\pm$1.2, $F(1,389)=19.24$, $p<0.0001$) and QIDS item 2 (CGT: BL 2.1$\pm$0.9 to EP 1.6$\pm$1.0 vs. No CGT BL 2.0$\pm$1.0 to EP 1.8$\pm$1.0, $F(1,384)=6.66$, $p=0.0102$), while medication had no effect (medication vs. placebo; PSQI-TS: $F(1,389)=0.64$, $p=0.42$; QIDS item 2: $F(1,384)=1.48$, $p=0.23$). Additional analyses examining patterns of change in sleep over time with treatment will be presented.
Conclusions: Subjective sleep improved significantly more with CGT than with pill placebo or citalopram alone in adults with CG.
Supported By: The initial clinical trial had the following funding sources: R01MH60783, R01MH085297, R01MH085288, R01MH085308, and P30 MH90333 from the National Institutes of Health and by grant LSRG-S-172-12 from the American Foundation for Suicide Prevention.
Keywords: Sleep, Bereavement, Therapy, Clinical-Trial, SSRI

F2. Deconstructing Inflammation in Posttraumatic Stress Disorder: A Study of C-Reactive Protein in Iraq and Afghanistan Veterans

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Background: Elevated inflammation may play a causal role in the development of posttraumatic stress disorder (PTSD) symptoms, and in PTSD-related increased risk for cardiovascular, autoimmune, and neurodegenerative diseases. Although a number of studies have linked PTSD with elevated inflammation, most prior studies of inflammation in PTSD have relied on small case-control designs and no previous studies have compared levels of inflammation in PTSD versus other psychiatric disorders.
Methods: Here, we examine whether PTSD and other psychiatric disorders are associated with elevated high sensitivity CRP (hsCRP) in a large sample of 16,587 Iraq and Afghanistan veterans (M age = 34.5$\pm$8.7 years; 15% women) by comparing hsCRP levels among veterans with PTSD (54%), other psychiatric disorders (25%) and no psychiatric diagnoses (21%). Data were compiled from VA administrative databases. Generalized linear models were used to ascertain differences among groups in log-transformed hsCRP, and the adjusted relative risk (ARR) for clinically high ($>$ 3mg/L) hsCRP. All models were adjusted for age, race, marital status, education, and body mass index (BMI).
Results: Veterans with PTSD had higher hsCRP than veterans with no or other psychiatric diagnoses. Veterans with psychiatric diagnoses other than PTSD also had higher hsCRP than those with none. Risk for clinically high hsCRP was increased in both veterans with PTSD and other psychiatric disorders. Among other psychiatric disorders, depression, anxiety, and alcohol-use disorders were associated with elevated hsCRP.
Conclusions: Results replicate findings of elevated inflammation in PTSD, but also highlight the transdiagnostic relevance of inflammation in psychiatry.
Supported By: NIMH K01; MIRECC
Keywords: PTSD - Posttraumatic Stress Disorder, Inflammation, War Veterans, C-reactive Protein, Transdiagnostic

F3. Imaging Alpha7 Nicotinic Acetylcholine Receptors in Individuals With PTSD

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Background: Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder, yet the underlying neurochemical factors are largely unknown. α7 nicotinic acetylcholine receptors (nAChRs) exist on glutamatergic neurons connecting the medial prefrontal cortex (mPFC) with the amygdala and hippocampus. These receptors drive plasticity in this important circuit involved

in fear response, stress, and PTSD. Here, we aimed to measure $\alpha 7$ nAChRs in PTSD and controls with positron emission tomography (PET) brain imaging.

Methods: To date, PET scans were acquired in 6 individuals with PTSD (PCL-S Scores = 60±11) and 7 age-matched controls. The $\alpha 7$ nAChR specific radioligand [18F]ASEM was injected as a 323±81 MBq bolus. Imaging data and metabolite-corrected arterial blood samples were collected for 120 min. $\alpha 7$ nAChR availability was indexed by the total distribution volume (VT), estimated using multilinear analysis in brain regions of amygdala, hippocampus, and mPFC.

Results: Regional [18F]ASEM VT values (units of mL/cm3) in individuals with PTSD vs. controls, respectively, were as follows: (23.9±0.9 vs. 27.0±3.4 in amygdala; 20.2±2.1 vs. 22.6±2.6 in hippocampus; 22.6±3.5 vs. 24.2±2.1 in mPFC). An unpaired t-test (uncorrected for multiple comparisons) suggested lower VT in amygdala for individuals with PTSD compared to controls ($p=0.046$). No evidence for relationships between [18F]ASEM VT and PCL-S score was found.

Conclusions: These preliminary findings merit further investigation into the role of $\alpha 7$ nAChRs in PTSD.

Supported By: K01AA024788; K01MH092681; K02DA031750; R01MH110674; VA National Center for PTSD

Keywords: PTSD, Alpha7 Nicotinic Receptor, PET Imaging

F4. Alzheimer's Disease Biomarkers are Associated With Altered White Matter Microstructure

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Background: Alzheimer's disease (AD) is characterized by the accumulation of beta amyloid plaque and neurofibrillary tangles. Additionally, several studies indicate that dementia due to Alzheimer's involves loss of local connections between neurons and connections between distal brain regions. However, the extent to which amyloid is accompanied by neural injury and loss of connectivity is unclear. Thus, in this study we investigated whether amyloid accumulation (indexed by amyloid PET imaging) was associated with altered white matter microstructure measured with multi-shell diffusion-weighted imaging (DWI).

Methods: Cognitively unimpaired participants (n=66) underwent [11C] PiB PET imaging for quantifying plaque deposition and multi-shell DWI. Indices from several DWI modeling techniques were generated and values were extracted from white matter tracts known to be affected by AD. These DWI values were used as dependent measures in linear regressions, where cortical PiB binding globally and in several AD-signature regions were used as predictors of interest. Age, sex, and APOE $\varepsilon 4$ positivity were included as covariates.

Results: PiB binding was associated with lower values of neurite density (NDI) and orientation dispersion (ODI) in the cingulum bundle (Figure 1), as well as radial, axial, and mean kurtosis, where higher amyloid was associated with lower microstructure integrity.

Conclusions: Amyloid burden is associated with altered white matter microstructure, even among people who are cognitively unimpaired. Although the directionality of these results must be further investigated, this study suggests that loss of connectivity is an early feature of AD, and that employing sensitive imaging measures may further inform the neuropathological disease course.

Supported By: This project was supported by NIH grants R01AG037639 (BBB), AG027161 (SCJ), P50 AG033514 (SA), the UW Institute for Clinical and Translation Research grant 1UL1RR025011, the Geriatric Research, Education, and Clinical Center (GRECC) of the William S. Middleton Memorial Veterans Hospital, the Swedish Alzheimer Foundation (# AF-553101 and AF-646211), the Torsten Söderberg Foundation (KB), the Research Council of Sweden (project #14002) (KB), the Swedish Brain Foundation (project # FO2015-0021) (KB), LUA/ALF Västra Götalandsregionen (VGR) Sweden (project # ALFGBG-139671) (KB), Swedish Research Council (#2013-2546) (HZ), the European Research Council (#681712) (HZ), Swedish State Support for Clinical Research (#ALFGBG-441051) (HZ), the Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow 2013) (HZ), and the National Science Foundation Graduate Research Fellowship under Grant No. DGE-1256259 (APM).

Keywords: Alzheimer's Disease, MRI Brain Imaging, Connectivity, Biomarkers, Amyloid Imaging

F5. Brain Disorders are Associated With Increased Brain Age

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Background: A wide range of clinical, cognitive, genetic and socioenvironmental factors contribute to mental illness and other brain disorders. This may suggest common pathways across brain disorders and dynamic processes influencing brain structure and function across the lifespan.
Methods: Here, we studied structural brain images from 31,887 individuals aged 3 to 97 years. We trained an age prediction machine learning model on cortical and subcortical features from 21,023 controls and predicted the age of individuals with dementia spectrum, psychosis spectrum, major depressive, autism spectrum and attention deficit disorders in an independent test set. Furthermore, we assessed SNP-based heritability of the deviance between brain age and chronological age in a subset of 12,550 healthy individuals of which genetic data was available.
Results: We found that many brain disorders are associated with increased brain age, with particularly strong effects observed in schizophrenia and Alzheimer's disease, and that the deviance from chronological age is heritable. Increased brain age in schizophrenia was mostly driven by fronto-temporal aberrations, whereas subcortical regions contributed strongest to the increased brain age in Alzheimer's disease.
Conclusions: Together, our results suggest that brain age represents a genetically influenced trait with great potential as an intermediate phenotype in the clinical neurosciences. Further, the large-scale case-control analysis strongly supports that individuals with common brain disorders show diverging life-span brain structural trajectories which may reflect common mechanisms across disorders with links to neurodevelopmental and aging-related processes, highlighting the relevance of a dynamic lifespan perspective when studying brain disorders.
Supported By: Research Council of Norway, South-Eastern Norway Regional Health Authority, KG Jebsen Foundation, European Commission 7th Framework Programme, National Institute of Health, National Institute of Mental Health, German Research Foundation, Swedish Research Council, Norwegian Extra Foundation for Health and Rehabilitation, Medical Research Council (UK), The Wellcome Trust, Department of Health for England and Wales, North West Regional Development Agency and the Scottish Executive, Biotechnology and Biological Sciences Research Council.
Keywords: Brain Age, Structural Brain Imaging, Brain Disorders, Heritability, Life-Span Trajectories

F6. Is it Possible to Elicit Progressive Functioning Decline Without Having Beta-Amyloid Pathology? Clinical Trajectories of Mild Cognitive Impairment With Suspected Non-Alzheimer's Pathology

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Background: Suspected non-Alzheimer's disease pathophysiology (SNAP) defines individuals with evidence of neurodegeneration (e.g. cortical hypometabolism) without Aβ. Findings from previous studies on clinical and structural trajectories of SNAP have been inconsistent.
Methods: Mild cognitive impairment (MCI) patients were categorized into four groups: amyloid only (Aβ+HYPO-), amyloid positive and hypometabolism (Aβ+HYPO+), no amyloid nor hypometabolism (Aβ-HYPO-), and SNAP (Aβ-HYPO+). Aβ+HYPO- (n = 34), Aβ+HYPO+ (n= 29) and Aβ-HYPO- (n = 36) groups were matched to SNAP on age, gender, apolipoE4 (apoE4) protein genotype, and global cognition. Elderly controls (n = 40) were matched to SNAP on age, gender, and apoE4 genotype. Baseline clinical profiles, changes in hippocampal volume changes, clinical symptoms of dementia, daily functions, and cognitive function over 2 years period were assessed.
Results: At baseline, there was no difference in function and cognition between SNAP and Aβ+ groups (Aβ+HYPO+ and Aβ+ group). SNAP showed worse symptoms of dementia and functioning at baseline than Aβ-HYPO- and controls. SNAP showed lower cerebrospinal fluid total tau and p-tau than Aβ+HYPO+ and Aβ+HYPO-. There was no difference in bilateral hippocampal volume changes between SNAP and all comparison groups. SNAP showed worse functioning deterioration than Aβ-HYPO- and controls. Aβ+HYPO+ showed more exacerbation in symptoms of dementia than SNAP.
Conclusions: Having cortical Aβ and hypometabolism may result in the worst clinical outcomes. It may be possible to promote progressive functioning deterioration without Aβ, bringing out the importance to examine pathways that may be mediated by biomarkers other than Aβ to investigate mechanisms underlying Aβ-independent functioning decline in MCI.
Supported By: CIHR Doctoral Award
Keywords: Aging, Hippocampus, Amyloid Imaging

F7. Investigating Interactions Between Reward and Threat Processing as Mechanisms Underlying Costly Fearful Avoidance Behaviour Using Startle Reflex Methodology

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Background: Fearful avoidance behaviour is a critical symptom across anxiety disorders and an important predictor of clinical outcome. However, little is known about how threat and reward appraisal interact to drive costly avoidance behaviour.
Methods: Forty-eight subjects could choose to approach or avoid situations differing in potential threat (threat of shock, no shock) and potential reward (€0.01, €0.1 euro, €0.50 euro, €1 euro) to create varying levels of approach-avoid conflict. As physiological markers of threat appraisal and reward appraisal, we respectively measured the eye-blink startle and the

post-auricular reflex (PAR) using electromyography during the build-up of decisions.
Results: Avoidance behaviour was significantly higher during threat ($p < .0001$) and decreased with level of potential reward ($p < .0001$). A significant threat X reward interaction-effect ($p = .002$) indicated that there was little modulation by reward in the safe condition where avoidance was low overall, while the modulation was strongly present in the threat condition. Eye-blink startle and PAR startle both demonstrated a threat X reward interaction ($p = .002$; $p < .0001$). Interestingly, within subjects' variation in PAR magnitude (but not eye-blink) significantly predicted trial-by-trial avoidance rates ($p < .0001$).
Conclusions: We successfully measured PAR and eye-blink magnitudes, as biological indicators of threat and reward appraisal respectively in a paradigm assessing approach-avoidance conflict. Results suggest that fluctuations in PAR but not eye-blink predict the modulation of avoidance behaviour. This is the first indication that a psychophysiological measure of reward appraisal may predict costly avoidance behaviour.
Keywords: Anxiety Disorders, Post-auricular reflex, Anxiety Potentiated Startle, Approach/Avoidance, Neurophysiology

F8. Individual Differences in Defensive Freezing Reactions Link to Anxiety, Cortisol and Performance Under Threatening Situations

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Background: In non-human animals, defensive freezing behavior is one of the most frequently used measures of threat responding, found to be related to anxiety behavior and altered HPA-axis functioning. In humans, defensive freezing can be also assessed but the predictive value for threat-related actions, anxiety and endogenous cortisol remain to be shown.
Methods: In a baseline measurement of a prospective study on stress-vulnerability, freezing behavior of 337 police recruits (at start of police education) and 82 healthy civilians were tested in an ecologically-valid shooting task. The shooting task is a speeded decision-making task under threat of shock which was performed on a stabilometric platform that measures body immobility. Hair strands were taken to index endogenous cortisol levels over the previous 3 months. The Spielberger Trait Anxiety Inventory (STAI) was used as a proxy for trait anxiety.
Results: The anticipation of shooting decisions under acute threat induced bodily freezing which was related to faster shooting ($Rs=0.183$, $p<0.001$) but also excessive shooting ($Rs= 0.181$, $p<0.001$). Stronger threat-induced bodily freezing predicted higher trait anxiety ($Rs= -0.119$, $p<0.05$) and lower hair cortisol ($Rs= 0.137$, $p<0.05$).
Conclusions: These findings show that human freezing levels predict defensive actions, in line with a critical role for freezing in action preparation. Moreover, freezing also predicts longer-term anxiety and HPA axis responses which suggests the relevance of freezing responses for stress- and anxiety related psychopathology.
Supported By: NWO-VICI
Keywords: Defensive Behavior, Freezing and Flight, Anxiety, Hair Cortisol, Psychophysiology

F9. The Computational Basis of Threat-Related Attentional Bias

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Background: Attentional bias towards threat is a consistent finding in anxiety disorders and is proposed to play a causal role in the development of symptoms. However, the origin of this bias remains unclear. In this study, we examine the influence of learning processes on visual attention, using a reinforcement learning model to identify components of the learning process whose abnormal operation may lead to a pathological attentional bias towards threat.
Methods: Subjects performed an aversive reinforcement learning task that involved learning to predict the occurrence of mild electric shocks. Eye tracking was used to monitor gaze location during the task to provide an index of visual attention. Computational models of learning were fit to behavioural responses and individual parameter estimates derived from these models were used to predict gaze position.
Results: Subjects exhibited biased attention towards stimuli currently perceived as having a high threat probability. Importantly, individual differences in parameters governing learning rates for shocks and shock omissions were associated with this subjective estimate of shock probability, suggesting that an attentional bias towards threat may develop as a result of a learning style that leads to a distorted estimation of the likelihood of negative outcomes.
Conclusions: This work highlights the importance of different learning processes underlying the allocation of visual attention, and suggests that the attentional bias towards threat seen in anxiety disorders could result from dysfunctional learning about threat in the environment. Future work will apply this computational framework to the study of clinical populations.
Supported By: Wellcome Trust
Keywords: Anxiety, Attentional Bias, Computational Psychiatry, Eye Tracking, Fear Learning

F10. Linking Emotional Control and Stress Reactivity: Anterior Prefrontal Cortex Activation During Emotion Control Predicts Cortisol Response After Stress Induction

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Background: The ability to control social emotional actions is relevant for everyday social interaction and may be predictive

of actual stress-responsiveness during social stress. Here we tested whether these processes are indeed interrelated, hypothesizing that reduced frontal control over emotional actions is associated with an increased cortisol response after subsequent stress induction.

Methods: 301 subjects (230 males) participated in an fMRI social-emotional approach-avoidance task, which involved impulsive and controlled emotional actions. Subsequently, participants underwent a socially evaluated cold-pressor task (SECPT), known to induce stress responses. Salivary cortisol levels were measured right before (baseline) and 10 mins. after the stress induction.

Results: In line with previous studies, participants showed slower reaction times, more errors and increased left anterior prefrontal cortex (aPFC) activation during emotion action control (left aPFC: $p = .006$, small-volume corrected). Moreover, cortisol levels were increased after subsequent stress induction ($t = 13.60$, $p < .001$). Most critically, bilateral aPFC activation during emotional control was negatively associated with this stress-induced cortisol response (left aPFC: $p = .005$, right aPFC: $p = .026$, small-volume corrected). No association between cortisol response and amygdala activation was found.

Conclusions: Reduced aPFC activation during instrumental control over approach-avoidance tendencies predicts increased cortisol responses after stress induction. This suggest a relationship between the ability to recruit prefrontal regions during social emotion regulation and the ability to regulate the hypothalamic-pituitary-adrenal(HPA)-axis activity during social stress-exposure. Ongoing longitudinal measurements within this sample will shed light on how these interrelated processes may contribute to the development of stress symptoms after traumatic events.

Supported By: Netherlands Organization for Scientific Research (NWO)

Keywords: Corticosteroid Stress Hormones, Emotion Regulation, Prefrontal Cortex, Psychosocial Stress, Social Behavior

F11. Altered 'Default' Processing in the Brain Predicts Individual Differences in Stress Reactivity

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Background: Acute stress has been linked to a re-allocation of brain resources resulting in shifts between large-scale brain networks, including default mode (DMN), salience (SN) and central executive (CEN) networks. However, whether individual differences in cortisol stress-responses link to dynamic reorganizations of those networks at rest remains unknown.

Methods: In the baseline measurement of a longitudinal study we investigated stress-induced functional connectivity changes (delta FC) of these resting-state networks by assessing resting-state fMRI scans before and after a formal stress induction (socially evaluated cold pressor test followed by a mental arithmetic task). A dual regression approach was used to investigate delta FC of each network at the individual level and permutation tests were used to investigate network changes after stress.

Results: Successful stress induction was indicated by increased salivary cortisol ($p<.001$), a-amylase ($p<.001$) and subjective stress levels ($p<.001$) in our sample ($N=361$). Further, increased as well as decreased functional connectivity of the target networks with wide-spread regions in the brain (i.e., occipital lobe, putamen) were observed after stress ($pfwe<.0125$). Most importantly, decoupling of the DMN regions ($Rs=-0.15$, $p=.0063$) and reduced synchronization between DMN and other brain regions ($Rs=0.16$, $p=.0037$) were associated with increased cortisol levels.

Conclusions: These results suggest that 'the default' processing of the brain is disturbed after stress and that the degree of this disturbance is associated with individual cortisol stress-responsiveness. These individual differences in neural stress-responses can potentially serve as a marker for stress-vulnerability, and will be further tested for their predictive value for symptom development in a follow-up study.

Supported By: VICI grant (#453-12-001) from the Netherlands Organization for Scientific Research (NWO)

Keywords: Stress Reactivity, Resting State fMRI, Default Mode Network, Predictive Biomarkers, Stress

F12. Bed Nucleus of Stria Terminalis (BNST) CRF Circuits for Anxiety-Like Behaviors

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Background: Human studies have implicated the bed nucleus of stria terminalis (BNST) in stress-related psychiatric diseases. Corticotropin-releasing factor (CRF) is a central regulator of the stress response, modulates aversive behaviors and neurons that express CRF are present in the BNST. In addition, a large body of preclinical literature implicates the CRF system in pathological emotional states associated with anxiety. However, a causal role for the BNST CRF cells and local circuitry in anxiety-like behaviors remains unclear.

Methods: Here we used transgenic tools, immunohistochemistry, in vitro electrophysiology, optogenetics and behavioral paradigms to examine the role of BNST CRF cells in anxiety and chronic stress-induced anxiety in male mice.

Results: Within the BNST, we find two populations of neurons; one that express CRF and a non-overlapping population group that express PKC-δ in male mice. We show that acute exposure to a novel environment results in increased activation of BNST PKC-δ cells. In contrast, chronic stress potentiates the activation of BNST CRF cells while decreasing activation of PKC-δ cells, that might underlie increased anxiety. We find that acute optogenetically mediated activation of BNST CRF cells during testing is sufficient to mimic chronic stress-induced anxiety-like behaviors. We are currently working on determining whether the activity of BNST CRF cells is necessary for chronic-stress induced anxiety.

Conclusions: Together, this data suggests that these two separate populations within the BNST are differentially recruited in response to chronic stress and that BNST CRF cells play a key role in chronic stress-induced anxiety.
Keywords: BNST, Chronic Stress, Anxiety, CRF

F13. Arousal and mPFC Activity in a Mouse Model of Acute Traumatic Stress

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Background: Pupillary dilation has recently been investigated as a potential biomarker for hyperarousal in PTSD. Separately, mechanistic studies in rodents have demonstrated that the pupil's diameter correlates tightly with the activity of individual neurons across cortical regions. Furthermore, locus ceruleus activity induces pupillary dilations.
Methods: Using an established model of acute traumatic stress (Stress-Enhance Fear Learning), we evaluated spontaneous and auditory-evoked pupillary dilations in stressed and unstressed animals. We also performed in vivo calcium imaging of neurons in the prelimbic prefrontal cortex of animals exposed to stress.
Results: Spontaneous fluctuations in pupillary dilation were increased in both male (n=10 stressed; n=10 controls) and female (n=7 stressed; n=7 controls) mice following stress. We estimated correlations between mPFC neuron activity and pupillary diameter in stressed and unstressed male mice.
Conclusions: By measuring pupillary dilations pre- and post-stress, we demonstrate a causal role for acute stress in altering pupillary fluctuations. This supplements previous work on pupillary dilation in PTSD, and demonstrates the feasibility of measuring stress-induced changes in arousal state at the level of individual neurons. Circuit-level manipulations of arousal state may further validate pupillary dilation as a translational biomarker.
Supported By: National Institute of Mental Health grant R01MH112750 (A.C.K.), National Institute of Mental Health grant R21MH110712 (A.C.K.), NARSAD Young Investigator Award (A.C.K.), and Inscopix DECODE award (A.C.K.), T32MH019961 (APK), T32MH014276 (APK), R25MH071584 (APK), Thomas P Detre Fellowship (APK)
Keywords: PTSD - Posttraumatic Stress Disorder, Hyperarousal, Neural Circuits, mPFC, Calcium Imaging

F14. Characterizing Neurotrophic Systems in the Primate Amygdala That are Relevant to Mediating and Treating Anxiety Disorders

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Background: Neuroplasticity is thought to be important in the pathophysiology of psychiatric disorders. We have reported on the relatively understudied neurotrophic factor system (NT3-TrkC) in the central nucleus of the amygdala (Ce) of young rhesus monkeys, where decreased levels of TrkC mRNA predicted high levels of anxiety, and increasing the activity of this system had anxiolytic effects. In the current study, we characterize the distribution of TrkC mRNA in the primate amygdala focusing on the Ce and explore TrkC function in an in vitro model of rhesus induced pluripotent stem cell (iPSC)-derived neurons.
Methods: We used in situ hybridization (N=10) and laser capture microdissection (LCM) with RNAseq (N=2), to characterize the expression of TrkC mRNA in brain regions of the rhesus monkey. To further explore TrkC mechanisms, we differentiated iPSCs into GABAergic, medium-spiny like neurons, similar to those found in the Ce, and recorded the electrophysiological effects of TrkC activation.
Results: Within the amygdala, RNAseq demonstrated that TrkC mRNA was expressed at higher levels in the basolateral amygdala than the Ce. TrkC in situ hybridization revealed a similar pattern for mRNA expression. The iPSC-derived neurons shared neuropeptide, transcription factor, and TrkC expression patterns with mature Ce neurons. Electrophysiology studies demonstrated that NT3 (0.05 μg/ml), the TrkC ligand, increased spontaneous action potentials by 228.2%.
Conclusions: These data provide a framework for future studies aimed at understanding mechanisms of, and new treatments for, human anxiety disorders. Additionally, the in vitro model of iPSC-derived, "Ce-like" neurons, is providing initial insights into mechanisms involved in modulating amygdala neuroplasticity.
Supported By: NIH R01MH046729; R01MH081884; P50MH100031
Keywords: Rhesus Monkey, Central Nucleus of the Amygdala, Anxious Temperament, Neurotrophins, NTRK3

F15. Fear Conditioning in Drug-Free OCD Patients Compared to Healthy Subjects: Preliminary Results

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Background: Obsessive-compulsive disorder (OCD) is characterized by repetitive thoughts and rituals which are frequently accompanied by exacerbated fear responses. Our aim was to investigate differences between drug-free OCD patients and healthy subjects regarding the classical fear conditioning paradigm.
Methods: Twenty-four drug-free OCD patients (13 women; mean age= 32, SD=8) and 14 healthy subjects (HS; 8 women; mean age=34, SD=13) were submitted to a two-day fear conditioning paradigm. Results were normalized as percent of maximum unconditioned skin conductance response (SCR) of each subject. The extinction retention index (ERI) was

calculated as described in previous trials. Additional indexes were calculated as ratios between the expected higher and lower mean SCR. Groups were compared using non-parametric tests. Spearman correlation was used to test associations between indexes.
Results: Nineteen patients and 10 HS passed SCR signal quality control. Patients and HS were not different regarding ERI (OCD median=78.9, SE=8.5; HS median=51.5, SE=11.4; overall median=59.2, SE=6.7). Eleven (58%) patients and 4 (40%) HS had ERI above the median. No differences were found between groups regarding indexes for learning or extinction (Median Test). OCD patients showed a trend toward stronger discrimination of context during recall and renewal than HS (p=0.07, Median Test). Higher context discrimination during presentation of the conditioned/extinguished stimulus was associated with better extinction efficiency (p=0.02, Rho=0.547, Spearman correlation).
Conclusions: In this preliminary analysis we were unable to replicate previous findings regarding low ERI in OCD patients compared to HS. However, we observed that the hole of context during fear learning might differ between OCD patients and HS.
Supported By: FAPESP, CNPq
Keywords: Obsessive Compulsive Disorder (OCD), Working Memory fMRI, Fear Conditioning

F16. The Neurobehavioral Basis of Anticipated Regret and Reward in Risky and Ambiguous Decision-Making in Generalized Anxiety Disorder

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Background: Despite considerable comorbidity, value-based decision-making research in anxiety and depression is often domain-specific (i.e., focus on threat in anxiety and on reward in depression). Notably, limited work on reward processing in individuals with anxiety has suggested an association with both loss and risk aversion to varying extents.
Methods: We compared neural activity and choices among 16 unmedicated patients with Generalized Anxiety Disorder to 16 demographically-matched controls in a win-only forced choice gambling task, wherein 50% of the trials exhibited ambiguous probabilities. We contrasted risk and ambiguity attitudes under Prospect Theory (PT) and Regret Theory (RT) in behavioral and fMRI data.
Results: Anxiety patients made significantly more risky and ambiguous choices ($p < .05$), a result potentially explained by significant correlations of risk and ambiguity aversion with anticipated regret. No significant neural differences were apparent in subjective value-related activity under PT, but medial temporal lobe, somatomotor cortex, and dorsolateral prefrontal cortex were all more active in controls relative to patients in RT modeling of subjective value under ambiguity, while patients exhibited greater activity in the precuneus (commonly associated with default mode activity). There was significantly more activity in controls related to anticipated rejoicing from RT among a number of regions, including anterior insula.
Conclusions: Anxious individuals overemphasize anticipated regret and underemphasize anticipated rejoicing relative to demographically-matched controls, when making decisions about uncertain reward. Anticipated regret has the capacity to explain both anticipated negative affect, as well as loss and risk aversion in anxiety.
Supported By: Professional Staff Congress of the City University of New York
Keywords: Anxiety, Decision Making, Computational Psychiatry, BOLD fMRI, Neuroeconomics

F17. Complex Dynamics of the Error-Monitoring System Reveal Insights Into Social Anxiety Within Structured and Unstructured Social Settings

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Background: Neural circuits associated with error monitoring are known to relate to anxiety. However, the degree to which complex time-frequency dynamics of the error-monitoring system relate to social anxiety, particularly within real-world settings, remains unclear.
Methods: EEG was recorded from 126 adolescents performing a flanker task twice, once under social observation and once alone. Response-locked time-frequency surfaces were calculated and theta power and inter-trial phase synchrony (ITPS) within the theta band were extracted for error and correct responses. Adolescent behavior was observed within two additional social contexts: a structured social setting that involved giving a speech, and an unstructured social interaction where the adolescent was left alone with two other children.
Results: Theta power (signal strength) and ITPS (signal consistency) increased for errors, compared to correct responses. Moreover, theta power ($t = 2.53$, $p = .012$) and ITPS ($t = 3.66$, $p < .001$) were increased for errors committed under social observation. Greater consistency of the error signal (theta synchrony), specifically within the social task, was associated with observations of increased anxiety within the unstructured social interaction ($r = .196$, $p = .042$). In contrast, increased strength of the error signal (theta power) within the social—relative to non-social condition—was predictive of reduced anxiety when delivering a speech ($r = -.221$, $p = .026$).
Conclusions: These data illustrate the importance considering complex time-frequency dynamics of the error monitoring system in relation to social anxiety. Moreover, the current results may shed light on subdomains of social anxiety, namely, generalized social anxiety as compared to performance anxiety.
Supported By: NIMH; NSF; NICHD
Keywords: Social Anxiety Disorder, Error Monitoring, Time-frequency EEG, Trier Social Stress Test

F18. Do Fear of Movement and Negative Cognitions After Trauma Lead to Activity Avoidance, Depression, and Chronic Posttraumatic Pain Development? Testing the Fear-Avoidance Model Using a Large Prospective Cohort

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Background: The most common model of chronic pain (CP) development posits that fear of movement and negative cognitions in the acute aftermath of injury lead to activity avoidance and depression, which in turn cause CP. However, this Fear-Avoidance Model (FAM) has rarely been tested empirically.
Methods: Participants enrolled after presenting to the emergency department (ED) following a motor vehicle collision (MVC). ED evaluation included assessment of pain (0-10 NRS), pain catastrophizing (PCS), and fear of movement (TSK, FABQ). Six-week assessment included depressive symptoms (CESD) and six-month assessment evaluated CP outcomes. Structural equation models (SEM) was used to determine whether FAM provided a good fit to the data and to evaluate hypothesized FAM relationships.
Results: Acute severe pain was common (mean 7.4 (SD = 2.2)) among participants (n=927, 62% female). Acute pain, pain catastrophizing, pain interference, and depressive symptoms were all included in the FAM SEM, but only acute pain (β= .308, <.001) and pain interference with normal work (β= .413, p<.004) contributed significantly to the prediction of CP. Negative cognitions (pain catastrophizing) in the aftermath of an MVC and depressive symptoms six weeks after an MVC did not predict chronic pain severity.
Conclusions: The FAM provided a poor fit to the data, and many relationships proposed in the FAM were not supported. Further studies are needed to better understand relationships between acute pain, negative cognitions, depressive symptoms, and the development of CP after common traumatic events such as MVC.
Supported By: R01AR060852
Keywords: Chronic Pain, Structural Equation Models, Fear-Avoidance Model, Depression, Trauma

F19. Avoidance, Hyperarousal, and Re-Experiencing After Motor Vehicle Collision Share a Common Vulnerability Substrate

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Background: Research evaluating dimensions of posttraumatic stress symptoms (PTSS) has been mixed; with some studies suggesting a common higher-order vulnerability factor that drives first order factors (e.g., re-experiencing, avoidance, and hyperarousal symptoms).
Methods: Participants presenting to one of nine emergency departments within 24 hours of motor vehicle collision (MVC) were enrolled. Symptoms of PTS (IES-R) were assessed at 6 weeks and 6 and 12 months. Models of avoidance, hyperarousal, and re-experiencing symptoms over time were developed, with and without an additional higher-order latent factor representing common vulnerability. Goodness of fit of competing models were compared. Subsequent structural equation modeling (SEM) evaluated characteristics influencing the higher order vulnerability factor.
Results: Follow-up rates at 6 weeks and 6 and 12 months after MVC among participants (N = 948) were 91%, 89%, and 91%, respectively. Models of PTS symptom clusters among those with follow-up data (N = 854, 63% female, mean age 36.1 (SD = 13)) identified three first-order factors representing distinct domains of PTSS (re-experiencing, avoidance, and hyperarousal symptoms) with good fit. Lower-order factors were regressed on a higher-order factor representing underlying vulnerability; this model fit the data well (χ^2(62) = 278.43, p <.001, RMSEA = .06, BIC = -140.43). In a full SEM, female sex (β= .275, p < .001) and possessing one or more copies of the FK506 risk allele (β= .175, p<.003) influenced the higher-order latent vulnerability factor.
Conclusions: These data suggest the importance of shared vulnerability to the development of re-experiencing, avoidance, and hyperarousal symptoms after MVC.
Supported By: R01AR056328
Keywords: PTSD - Posttraumatic Stress Disorder, Structural Equation Modeling, Avoidance, Hyperarousal, Motor Vehicle Collision

F20. Aversive Value Generalization During Human Avoidance Learning Predicts Anxiety

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Background: Generalization during aversive decision-making allows us to avoid a broad range of potential threats following experience with a limited set of exemplars. However, overgeneralization, resulting in excessive and inappropriate avoidance, has been implicated in a variety of psychological disorders, including anxiety and obsessive-compulsive disorders.
Methods: Here, we investigated the mechanisms underlying generalization in avoidance behaviour in two groups of participants (N=26 lab-based neuroimaging sample; N=482 general population online sample). We used reinforcement

learning modelling in conjunction with robust multivariate analysis of neuroimaging data to associate different algorithmic components of avoidance generalization with regional brain circuitry (sample one) and self-reported psychological symptom scores (sample two).
Results: We found that generalization of avoidance could be parsed into perceptual and value-based processes, and further, that value-based generalization could be subdivided into that relating to aversive and neutral feedback - with corresponding circuitry including primary sensory cortex, anterior insula, and ventromedial prefrontal cortex, respectively ($p \leq 0.029$ precision-weighted multiple linear regression models, testing association between individual estimates of relevant model parameters and the cross-validated multivariate representational distance between conditioned stimuli and generalization stimuli in each brain region). Further, generalization from aversive, but not neutral, feedback was selectively associated with greater self-reported anxiety and intrusive thoughts ($p=0.008$ precision-weighted multiple linear regression model, testing association between individual parameter estimates and factor analysis-derived psychological symptom scores, corrected for age and gender identity).
Conclusions: These results reveal a set of distinct mechanisms that mediate generalization in avoidance learning, and show how specific individual differences within them can yield anxiety.
Supported By: Wellcome Trust
Keywords: Reinforcement Learning, Computational Psychiatry, Anxiety Disorders, Fear Generalization, Obsessive Compulsive Disorder (OCD)

F21. Standard Antidepressant Therapy in Posttraumatic Stress Disorder (PTSD) is Associated With a Higher Odds of Externalizing Behaviors and Homicidal Ideation: Results From the US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS)

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Background: Irritable behavior and angry outburst (DSM-5 Criterion E.1) can be features of alteration in arousal and reactivity in PTSD. We examined post-marketing individual safety reports(ISR) of externalizing behaviors(EB) and homicidal ideation(HI) in PTSD patients where sertraline, paroxetine, fluoxetine, or venlafaxine (SER_PAR_FLU_VEN) (US Department of Defense recommended pharmacotherapies for PTSD) were reported as primary suspect (PS).
Methods: We studied 9,553,117 ISRs using the FAERS database from January 1,2004-June 30,2017. Medical Dictionary for Regulatory Activities 19.0(MedDRA) preferred terms (PTs) were used to identify ISRs which specified PTSD (10036316) (MedDRA code) as the indication of interest, and externalizing behaviors (EB) (including aggression [10001488], anger [1002368], antisocial behavior [1002820], hostility [10020400], irritability [10022998])or homicidal ideation(HI) (10049666),as adverse events. Reporting odds ratios (ROR) with 95% confidence intervals (CI) were calculated to assess baseline risk for EB and HI when SER_PAR_FLU_VEN were used for PTSD versus other indications.
Results: There were 4,776 ISR with PTSD as indication and SER_PAR_FLU_VEN as PS. For EB the RORs were: PTSD versus all other indications:1.514 (95% CI 1.273-1.801; $z=4.692$, $p<0.0001$); PTSD versus depression: 1.569 (95% CI 1.317-1.869; $z=5.046$, $p<0.0001$). Similarly, for HI the RORs were: PTSD versus all other indications: 4.008 (95%CI 2.610-6.156, $z=6.342$, $p<0.0001$); PTSD versus depression: 3.908 (95% CI 2.521-6.059; $z=6.094$, $p<0.0001$).
Conclusions: Our disproportionality analysis generated potential safety signals of EB and HI which were more pronounced when SER_PAR_FLU_VEN were used for PTSD versus all other indications or depression alone. This may indicate the activating effect of SER_PAR_FLU_VEN superimposed upon the already autonomically dysregulated/sympathetically aroused state in PTSD.
Keywords: Antidepressants, PTSD - Posttraumatic Stress Disorder, Autonomic Reactivity, Aggression, Homicidal Ideation

F22. Understanding the Patient Experience of Psychiatric Neurosurgery for Intractable Obsessive Compulsive Disorder

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Background: A small subset of patients with Obsessive Compulsive Disorder (OCD) undergo neurosurgery for intractable illness. Despite this, little is known about the experiences of these individuals pre- and post-neurosurgery.
Methods: We conducted semi-structured interviews with 6 participants (4 responders, 2 non-responders) after Gamma Ventral Capsulotomy (GVC) for OCD. Patient interviews were analyzed for common language/narratives through Interpretive Phenomenological Analysis, a well-established method of qualitative analysis designed to capture patients' lived experiences.
Results: All interviewees demonstrated significant concordance in narratives: 1) After years of conventional treatments, patients felt neurosurgery was their "last hope" and described themselves as "desperate." 2) All exhibited code-switching between the medical/scientific and supernatural/religious lexicons, with some describing the surgery as "magical." 3) Post-surgery, subjects described fear/worry as they waited for improvement, consistent with literature on Gamma Knife for other indications. 4) Patients that improved described it as losing an "enemy" in the brain and stated they had or were planning to discontinue psychiatric treatment, despite

extensive cautions. 5) Patients that had not improved described themselves as "depressed" and "hopeless."
Conclusions: This is the first study examining the lived-experience of patients undergoing GVC for OCD. Ethicists have noted that patients receiving psychiatric neurosurgery are a uniquely vulnerable population given desperation for surgery. These data suggest patients are desperate, perhaps out of fear that surgery is a last option. This perception may lead those who improve after surgery to discontinue standard treatment, despite clinical advice. More attention may need to be given to these two issues in pre- and post-operative management.
Supported By: 5K23MH100607
Keywords: Obsessive Compulsive Disorder (OCD), Psychiatric Neurosurgery, Narrative, Subjective Experience

F23. A Literature Review of Human Studies on Neuropeptide Y (NPY) in Posttraumatic Stress Disorder (PTSD) or Substance Use Disorder (SUD)

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Background: Researchers are becoming more interested in how Neuropeptide Y (NPY) is involved in PTSD or SUD. Research methodologies have primarily focused on associations between NPY levels and these psychopathologies or NPY gene studies in PTSD or SUD. The report reviews the current state of literature about NPY in these prevalent disease states.
Methods: SCOPUS and PUBMED Central databases from 1970 to beginning of December 2017 were queried for the term, NPY, and a combination of other search terms for posttraumatic stress disorder, substance use disorder, alcohol use disorder, association study, gene study.
Results: There was a low yield of human clinical research. For "Clinical AND NPY AND PTSD", PUBMED Central yielded 366 papers with 63 being relevant to the topic (17.21%). In contrast, with the same search terms, SCOPUS yielded 19 papers with 14 being pertinent (73.68%). NPY is known to affect the HPA, amygdala and locus coeruleus which are involved in stress and addiction. Studies with human participants found that: NPY levels are decreased in individuals with PTSD versus controls; there is an unclear relationship for NPY levels and substance use disorders; and, there are inconsistencies in NPY genetic alleles for both.
Conclusions: A gap in clinical research remains for neuropeptide Y with PTSD and SUD. Besides a replicated association of NPY levels with PTSD, other findings of NPY with SUD are inconsistent.
Keywords: NPY, PTSD - Posttraumatic Stress Disorder, Substance Use Disorder, Substance-Related Disorder, Genetics

F24. Proton Brain GABA in Veterans With Posttraumatic Stress Disorder (PTSD)

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Background: Veterans are at increased risk of developing PTSD resulting from a number of factors including military-related combat. Structural and functional neuroimaging studies in patients with PTSD have demonstrated alterations in the anterior cingulate cortex (ACC). Altered Gamma-amino-butyric acid (GABA), the principal inhibitory neurotransmitter and modulator of neuronal excitability, has been implicated in PTSD. However, studies of ACC GABA in veterans are scarce. The current study investigated differences in GABA in veterans with and without PTSD using proton magnetic resonance spectroscopy (1H-MRS).
Methods: Twenty-seven veteran participants with PTSD and 45 veterans without PTSD, ages 24 to 54, completed a diagnostic interview and a scanning protocol on a 3T Siemens VerioTM whole-body MRI scanner. Single-voxel MRS data were acquired from an ACC voxel and quantified using the ProFit algorithm.
Results: Student's t-test with Welch's correction indicated that veterans with PTSD exhibited significantly lower GABA/H2O in the ACC compared to veterans without PTSD ($p < 0.05$). Second, HAM-A scores were negatively correlated with GABA/H2O in the non-PTSD group but not in the PTSD group. In the PTSD group, HAM-A scores were positively correlated with glutamine/H2O. However, this finding was not observed in the non-PTSD group.
Conclusions: The results support a role for GABAergic alterations in the ACC as well as a potential dysregulation of the excitation-inhibition balance in the ACC in veterans with PTSD. These findings may be consistent with evidence of ACC hyperactivity at rest in PTSD. The results also suggest differential neurochemical correlates of anxiety in PTSD.
Supported By: This project is funded by the Military Suicide Research Consortium (MSRC), an effort supported by the Office of the Assistant Secretary of Defense for Health Affairs under Award No. W81XWH-10-2-0178; and through Merit Review 5I01CX000253-02.
Keywords: PTSD - Posttraumatic Stress Disorder, GABA, Veterans, Proton Magnetic Resonance Spectroscopy, Anxiety

F25. PTSD is Associated With Reduced Anterior and Posterior Hippocampal Connectivity in Combat Veterans

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Background: The hippocampus is a focus of posttraumatic stress disorder (PTSD) research. Functional magnetic resonance (fMRI) resting state functional connectivity (rs-fc) may reveal alterations in hippocampal anatomical and functional

neuronal connectivity, however few studies in PTSD have used rs-fc techniques that distinguish anterior and posterior subregions, despite their known functional and anatomical differences. To address this, we used masked independent component analysis (ICA) with dual regression to investigate PTSD-associated alterations in subregional hippocampal-brain rs-fc in a large sample of military veterans.
Methods: PTSD was diagnosed with the Clinician Administered PTSD Scale (CAPS) in 230 male and female military veterans. Resting state fMRI images (3T) were analyzed with ICA masked within the bilateral hippocampus to define 10 independent components (ICs) for whole brain dual regression. Resulting rs-fc of each IC was compared between 100 cases with PTSD (33.6±6.7 years, CAPS 24.1±10.9) and 130 controls without current or lifetime PTSD (31.4±7.9 years, CAPS 2.5±3.5), using randomise (FSL v6) with threshold free cluster enhancement, $p < 0.05$ family-wise error corrected.
Results: Resulting ICs occupied discrete anterior-posterior hippocampal subregions as in previous studies. PTSD was associated with reduced ($p < 0.05$) hippocampal-brain rs-fc in both anterior and posterior ICs: between the right anterior hippocampus IC and the bilateral amygdala, thalamus, ventral tegmental area, and multiple prefrontal cortex regions, and between the right and left mid and posterior hippocampal ICs and the bilateral precuneous and PCC.
Conclusions: Results suggest PTSD diagnosis is associated with reduced anterior and posterior hippocampal rs-fc, supporting hippocampal dysfunction as a biological underpinning of PTSD.
Supported By: Steven and Alexandra Cohen Veterans Center
Keywords: Anterior Hippocampus, Posterior Hippocampus, Posttraumatic Stress Disorder, Resting State, Functional Connectivity

F26. Probing Cognitive Control Neurocircuits: A Concurrent TMS-fMRI Investigation of State Dependence

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Background: Transcranial magnetic stimulation delivered concurrent with functional magnetic resonance imaging (TMS-fMRI) extends conventional correlational imaging to causal neurocircuit mapping. That is, single pulses of TMS can be delivered to superficial cortical regions, and the activity in the connected networks mapped with the BOLD response. In the current study, we investigated whether state dependence, particularly emotional arousal, would influence the responsiveness of the fronto-parietal network to single pulse TMS (spTMS).
Methods: Twenty-four healthy individuals completed a picture-viewing paradigm in the MRI scanner. Pleasant, neutral and unpleasant pictures from the International Affective Picture System were presented in blocks. While pictures were presented in the foreground, spTMS was delivered intermittently to left dorsolateral prefrontal cortex, the typical therapeutic target.
Results: Emotional picture processing increased BOLD responses to spTMS in bilateral fronto-parietal regions (i.e., left and right dlPFC and intraparietal sulci). Further, strong modulation of visual processing networks as a function of emotional arousal suggests that concurrent TMS did not disrupt processing of the foreground task.
Conclusions: Therapeutic rTMS is moving toward manipulating the cognitive/affective state of the patient during treatment delivery. This includes clinically-relevant immersive environments, visual cues, and imaginal exposure. The current findings suggest that increasing emotional arousal, in fact, increases activation in the distributed cognitive control network, particularly fronto-parietal regions. Taken together, these findings suggest that varying emotional arousal during rTMS may be a productive means of strengthening the response within the distributed cognitive control network.
Supported By: K23 MH104849
Keywords: TMS-fMRI, Emotion, Brain Stimulation

F27. Subcortical Volumes in Social Anxiety Disorder: Preliminary Results From Enigma-Anxiety

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Background: Although many studies have focused on subcortical volumes in social anxiety disorder (SAD), their findings are remarkably discrepant. Relatively modest sample sizes, differences in region-of-interest selection, and variations in clinical characteristics across samples may contribute to the mixed findings. Here, alterations in subcortical volumes in SAD were examined with a meta-analytic approach, in the largest sample to date.
Methods: T1-weighted scans from 404 SAD patients and 775 controls were segmented using FreeSurfer 5.3 across 14 adult cohorts. Subcortical segmentations were visually inspected for accuracy per ENIGMA protocols. In linear regression models, subcortical volumes were contrasted between patients and controls and related to anxiety severity in patients, as measured with the Liebowitz Social Anxiety Scale. Sex, age, and intracranial volume were included as covariates. Meta-analysis of effect sizes across samples was conducted using a Bonferroni-corrected threshold ($p<0.0036$; 0.05/14 regions).
Results: There were no significant differences in subcortical volumes between SAD patients and controls, but a trend was observed towards lower volume in the left thalamus (Cohen's D= -0.14, punc=0.05). SAD-patients with a higher symptom severity tended to have smaller volumes of right hippocampus (B=-3.53, 95%CI: -6.69,-0.36) and right amygdala (B=-1.73, 95%CI: -2.90,-0.56).
Conclusions: Subtle alterations in subcortical volumes may be present in adult SAD patients; these alterations appear to be slightly more pronounced in patients with a higher symptom severity. Higher-powered meta-analytic comparisons (N>1,000 SAD patients) are planned to gain more insight into clinical characteristics associated with brain morphometry.
Supported By: NIH BD2K U54 EB020403
Keywords: Structural MRI, Social Phobia, Thalamus, Meta-analysis, Harmonized Protocols

F28. Levels of Early-Life Behavioral Inhibition Temperament Predict Distinct Neurodevelopmental Pathways to Pediatric Anxiety Symptoms

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Background: Anxiety symptoms evolve as children approach adolescence. Individual differences in behavioral inhibition (BI), an early-life fearful temperament, may define distinct developmental paths through which anxiety symptoms arise. Prior cross-sectional research suggests that level of early-life BI moderates how later anxiety symptoms relate to attention and associated amygdala-prefrontal cortex (PFC) circuitry function. However, no study has examined longitudinal changes in these functions as they relate to anxiety, in children who manifested different BI levels. We tested whether levels of early-life BI predict distinct associations between anxiety symptoms and amygdala-PFC function across development.
Methods: 87 children were assessed for BI in toddlerhood. At 10 and 13 years, they completed assessments of anxiety and an fMRI-based dot-probe task including threat, happy, and neutral stimuli. Using linear-mixed-effects models, we investigated longitudinal changes in associations between anxiety symptoms and threat-related amygdala-PFC connectivity, as function of BI.
Results: In children with high early-life BI, anxiety symptoms became, with age, more negatively correlated with right amygdala-left dorsolateral-prefrontal-cortex (xyz=-19,21,39; 890mm3, F=6.26, p=0.0001) connectivity when attention was maintained specifically on threat (age-10: r=0.34, age-13: r=-0.40; Z=3.01, p=0.003). In contrast, low-BI children showed an increasingly positive anxiety-connectivity association (age-10: r=-0.30, age-13: r=0.49; Z=3.02, p=0.002). Behaviorally, anxiety related to decreased attentional stability in high-BI children, and increased attentional stability in low-BI children.
Conclusions: High early-life BI may predict evolving deficiency in threat-related amygdala regulation by PFC. In contrast, low-BI may predict enhanced regulation. These distinct trajectories differentially relate to anxiety symptoms with age, and may inform diagnosis and treatment applications.
Supported By: NIMH Intramural Research Program (ZIAMH002781-15, NCT00018057)
Keywords: Anxiety Disorders, Brain Imaging, fMRI, Longitudinal Brain Imaging, Behavioral Inhibition, Pediatric Anxiety

F29. Interactions Between Cognitive Control and Decision-Making Networks: A Potential Biomarker of Suicidality

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Background: Poor decision-making is inversely related to cognitive control, yet paradoxically, decision-making is less impulsive in high-lethality attempters when compared to less suicidal individuals. We therefore examined structural and functional characteristics of cognitive control regions in individuals with posttraumatic stress disorder (PTSD) to investigate the relationship between cognitive control and suicide risk.
Methods: Suicidality scores derived from the Inventory of Depressive Symptomatology-Self Report (IDSSR) and structural and resting state functional 3T MRI scans were collected from participants with PTSD (N=33, female=12, mean

age=50). Subject-level grey matter volume and functional connectivity statistics from cognitive control (ventrolateral, dorsolateral, frontopolar cortices) and decision-making (striatum, anterior cingulate, insula, orbitofrontal cortex) regions were entered into statistical models to evaluate their impact on suicidal severity. Results were false discovery rate corrected.

Results: Grey matter volume in left pars triangularis was positively associated with suicidal severity ($p<.005$). Functional connectivity of left triangularis to right insula ($p<.05$) was positively associated with suicidality. Functional connectivity between frontopolar cortex and control regions in left inferior frontal gyrus (including triangularis) were negatively correlated with suicidality (all $p<.05$). Post hoc correlations with other clinical symptoms were non-significant (all $p>.1$).

Conclusions: Greater structural integrity and inter-network connectivity was observed in regions implicated in interference resolution in more suicidal individuals. Functional interactions between triangularis and insula may facilitate overriding emotionally-driven decision-making and the construction of well-planned, more lethal suicide attempts. These preliminary results suggest that aspects of the cognitive control system are promising potential neuroimaging biomarkers of suicidality that warrant further investigation.

Supported By: This work was supported by an investigator-initiated grant from Neuronetics, Inc. to Butler Hospital (NSP, LLC) and Career Development Award Grant No. IK2 CX000724 (NSP) from the U.S. Department of Veterans Affairs (Clinical Sciences Research and Development) and the Center for Neurorestoration and Neurotechnology at the Providence VA Medical Center.

Keywords: Suicide, Functional Neuroimaging, Volumetric Neuroimaging, Cognitive Control Network, PTSD - Post-traumatic Stress Disorder

F30. Early Life Adversity is Associated With Enhanced Fronto-Limbic Reactivity During Fear Processing in Adults With Depression and Anxiety

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Background: Early life adversity (ELA) is a potent risk factor for psychopathology, including depression and anxiety disorders. ELA history is linked to alterations in neural phenotypes of threat processing in adulthood, however whether these neural abnormalities are trans-diagnostic, across multiple psychopathologies is not well understood.

Methods: 132 individuals, including 102 treatment-seeking adults with heterogeneous depressive and anxiety disorders and 30 healthy controls (HCs) performed an emotional face-matching task during fMRI. Patients with (n =52) and without (n=50) ELA were determined based on moderate or high elevations on the Childhood Trauma Questionnaire subscales. Whole brain results for the contrast of interest, Fear>Shapes, were family-wise error corrected at α less than .05 using a voxel threshold of $p<.001$ and minimum cluster size of 85 voxels. Extracted beta-weights were correlated with the Emotion Regulation Questionnaire (ERQ).

Results: Relative to patients without ELA and HCs, patients with ELA demonstrated increased activation in the right dorsolateral/dorsomedial prefrontal cortex, bilateral ventral anterior cingulate, posterior cingulate, left fusiform gyrus, and right precuneus during threat processing, controlling for current symptoms of depression and anxiety. Among patients with ELA, activation in the anterior cingulate was positively correlated with emotional suppression ($r=.28$, $p=.049$).

Conclusions: Results provide initial evidence that ELA history among patients with internalizing disorders augments engagement of brain regions involved in emotion processing, above and beyond what is accounted for by current symptoms. Though longitudinal designs are needed, alterations in the neural correlates of maladaptive regulatory responses to threat may be a common pathway by which ELA poses risk for subsequent psychopathology.

Supported By: NIMH R01MH101497

Keywords: Functional Neuroimaging, Internalizing Disorders, Childhood Trauma, Emotional Suppression, Emotional Facial Processing

F31. Affective Brain Signal Variability Separates Social Anxiety Disorder Patients From Healthy Individuals

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Background: Amygdala hyper-responsiveness to negative socio-affective stimuli have typically been demonstrated in patients with social anxiety disorder (SAD). Relative to conventional methods, there is emerging evidence that brain signal variability could be a better predictor of behavior than mean neural response.

Methods: We recruited 46 patients with SAD (mean age 31, 63% females) and 40 matched healthy controls (HC) to undergo 3 Tesla functional magnetic resonance imaging (fMRI) at 2 time-points, totaling 172 MRI sessions. Blood-oxygen level-dependent (BOLD-fMRI) was performed while viewing happy and fearful faces in blocks of 80 seconds. BOLD-fMRI data was reviewed by manually classifying signal from noise. Variability was calculated as each voxel's standard deviation on signal across scanning-time. Multivariate partial least squares (PLS) estimated patterns of variability that separates patient from controls.

Results: PLS found one significant latent variable with cross-block covariance on 64%, permutated (x 1000) $P<0.001$, bootstrapped 95% confidence intervals on each condition, demonstrating less signal variability to happy faces in patients, relative to controls. This pattern of response was spatially located in several regions across the whole-brain, with large clusters appearing in bilateral amygdala, medial prefrontal cortex and posterior cingulate cortex/precuneus.

Conclusions: We found that neural response variability to positive socio-affective stimuli accurately separated patients from controls. It is likely that less signal variability highlights a deficit in effective emotion processing. We add to the growing literature on healthy individuals suggesting that task-specific brain signal variability contains useful information. The brain signal variability approach opens new avenues to evaluate and better understand brain function in common psychopathology.
Keywords: Social Anxiety Disorder, BOLD fMRI, Variability

F32. TMS-EEG Biomarkers for Combat-Related PTSD

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Background: Combat-related PTSD is experienced by men and women who have been in combat. Despite the large proportion of veterans returning from war with PTSD. Little is known regarding the underlying circuit abnormalities that are responsible for residual post-traumatic symptoms. Lack of this knowledge currently impedes the ability to develop circuit-informed novel therapeutic interventions.
Methods: We performed concurrent single-pulse TMS-EEG (spTMS-EEG) to a large number of healthy controls (N= 80) and PTSD combat veterans (N = 80) who were deployed to either Iraq, Afghanistan, or both. Sites in key cognitive and emotional networks were stimulated. The EEG data were cleaned using our in-house fully automated artifact rejection algorithm [1]. The spatio-temporal dynamics following the spTMS were then examined. The EEG responses were quantitated using TMS-evoked potentials (TEPs) and event-related spectral perturbations (ERSPs) of the induced oscillations, in both the sensor and source spaces.
Results: Following the anterior DLPFC stimulation, significant differences were observed for the early (<100 ms) and late (>100 ms) TEPs and ERSPs between the PTSD and healthy control groups ($p < 0.05$, unpaired t-tests, FDR corrected for multiple comparisons). These changes were identified across a number of key regions within the central executive network, salience network, and default mode network.
Conclusions: These results reveal for the first time abnormalities of casual information processing in PTSD patients across key cognitive and emotional brain networks. These biomarkers are critical in understanding the mechanisms underlying PTSD. Potential future avenues of this work include development and personalization of rTMS to normalize these circuit abnormalities.
Supported By: Cohen Veterans Bioscience; Stanford Neurosciences Institute
Keywords: PTSD - Posttraumatic Stress Disorder, TMS-EEG, Noninvasive Brain Stimulation, Brain Networks, Neural Oscillations

F33. Feedback Modulated Changes in TPJ Connectivity in Subclinical Social Anxiety

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Background: During interpersonal interactions, socially anxious individuals have a tendency to overestimate the likelihood of social threat, such as rejection or betrayal. Abnormal processing in the temporoparietal junction (TPJ), a region implicated in social cognition, is believed to underlie the cognitive aberrancies that characterize social anxiety. The purpose of this study was to identify regions of the brain that exhibit connectivity with the TPJ during feedback appraisal during the iterated Prisoner's Dilemma task.
Methods: 31 non-psychiatric volunteers (Ages 18-28), categorized as having high or low trait anxiety using Liebowitz Social Anxiety Scale-Self Report (LSAS-SR) scores, were scanned while playing the iterated Prisoner's Dilemma task against a computerized confederate whom they were deceived to believe was a human co-player. BOLD data for all trials were examined using the Psychophysiological Interaction (PPI) analytic technique.
Results: Although significant differences between anxiety groups were not revealed in a voxel-wise analysis, a cluster-based analysis found that the bilateral TPJ exhibited a positive trend of increased connectivity to the superior temporal gyrus ($t(1,28)=3.96$, $p<.05$) in low compared to high anxious participants.
Conclusions: Contrary to original predictions about differences in effective connectivity associated with anxiety symptoms, low anxious actually exhibited a positive trend of activity in the STG. Strong interpretations cannot be made on these results given that they were extracted using a liberal cluster-based threshold of .05. Future research should be directed towards examining whether there are alternate nodes within the social cognition network which could indicate dysfunction in social anxiety based on alterations in effective connectivity.
Supported By: NSF
Keywords: Social Anxiety Disorder, Prisoner's Dilemma, Theory of Mind, Functional Brain Imaging

F34. Examining the Short-Term Anxiolytic Effect of Floatation-REST

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Background: Floatation-REST (Reduced Environmental Stimulation Therapy), a novel body-based intervention which attenuates exteroceptive sensory input to the nervous system, has recently been found to reduce state anxiety across a

diverse clinical sample with high levels of anxiety sensitivity (AS). To further examine this anxiolytic effect, the present study investigated the affective and physiological changes induced by Floatation-REST, and assessed whether individuals with high AS experienced any alterations in their awareness for interoceptive sensation while immersed in an environment lacking exteroceptive sensation.
Methods: Using a within-subject crossover design, 37 participants with high AS were randomized to undergo a 90-minute session of Floatation-REST or an exteroceptive comparison condition. Measures of self-reported affect and interoceptive awareness were collected before and after each session, and indices of blood pressure (BP) and heart rate variability (HRV) were collected during each session.
Results: Relative to the comparison condition, Floatation-REST generated a significant anxiolytic effect ($p<.001$ for all variables) characterized by reductions in state anxiety and muscle tension, and increases in feelings of relaxation and serenity. A significant reduction in BP ($p<.001$), on the order of ~13 mmHG, and an increase in normalized high frequency HRV ($p<.05$) was observed during the float session. The float environment also significantly ($p<.001$) enhanced awareness and attention for cardiorespiratory sensations.
Conclusions: Floatation-REST induced a state of physiological relaxation and heightened interoceptive awareness in a clinical sample with high AS. The paradoxical nature of the anxiolytic effect in this sample will be discussed in relation to Wolpe's theory of reciprocal inhibition.
Supported By: This research was supported by the William K. Warren Foundation and a grant from the Epsom Salt Council.
Keywords: Novel Intervention, Anxiety Sensitivity, Interoceptive Awareness, Anxiety Disorders

F35. From Trauma to Intervention to Validation: Mindfulness, Movement, and Arts Based Interventions for Refugees Having Experienced High Stress and Trauma

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Background: High trauma and stress in refugees necessitates interventions. Cultural beliefs limit acceptance of pharmacological interventions and access to psychotherapy is limited by language and cultural barriers. Also, in this population, mental pain is commonly conveyed somatically. There is evidence that dance/movement therapy (DMT), art, yoga, and high intensity interval training (HIIT) may reduce stress and somatic burden. However, the quantitative data, and neurophysiological understanding of the impact is lacking.
Methods: Refugees with high stress and trauma partake in 12 weeks of 90 minute weekly sessions in DMT or art (children ages 7-17), mindful yoga (women 18+), or HIIT training (men 18+). Cortisol levels (hair samples; associated with stress) and inflammation markers C-Reactive Protein, IL-1 & IL-6, and TNF alpha (blood samples for adults; saliva samples for children; all associated with PTSD, anxiety, and depression) are measured before, during, and immediately after treatment, as well as 3 and 6 month follow-up. We assess psychological state at the same time points.
Results: Pilot data on n=5 women (yoga) showed 29% decrease in somatic burden after the full intervention. We observed a 34% decrease in anxiety disorders in children (DMT; n=7). Biomarkers collected from the pilot group are currently being analyzed; a second intervention phase (n=15 to 30 per group) is in progress.
Conclusions: These interventions are well received by the population. Collection of biomarkers for validation of these interventions is feasible and, in conjunction with a full series of psychological data, will provide some of the first evidence of its kind for these treatments.
Supported By: Blue Cross Blue Shield of Michigan Foundation Student Award; Blue Cross Blue Shield of Michigan Foundation Investigator Award; Detroit Medical Center Foundation Grant
Keywords: PTSD - Posttraumatic Stress Disorder, Trauma, Depression and Anxiety, Cortisol, Inflammation

F36. Single-Shot Gamma Ventral Capsulotomy for Obsessive Compulsive Disorder and Insufficient Response to Radiosurgery

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Background: Gamma Ventral Capsulotomy (GVC) is a radiosurgical procedure employed in the treatment of refractory obsessive-compulsive disorder (OCD). Most studies have made double shot (ds) lesions on each hemisphere, with good efficacy and safety. However, a first study found that four of five patients responded to a safer radiosurgical procedure using smaller, single-shot (ss) lesions (Sheehan et al., 2013). Our aim was to replicate these findings in a different surgical facility.
Methods: Five refractory OCD patients received ssGVC, in a dose of 150 Gy, aiming the ventral border of the anterior limb of the internal capsule. Patients were followed-up for 12 months at least. If ssGVC was ineffective, patients could receive additional dorsal shots after one year. Periodical pre and post-operative follow-up assessments were provided, including psychopathological, global status, and neuropsychological scales, and neuroimaging.
Results: Contrary to our expectations, none of the five patients receiving ssGVC responded to treatment by month 12, with a median reduction of only 13.5% on the scores of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Later, in a median follow-up of 20 months, symptom reductions were even smaller (8.1%). After additional dorsal lesions were made, our preliminary findings suggest that

some patients showed considerable reductions of their Y-BOCS scores.
Conclusions: Contradicting a previous study, ssGVC was not efficacious for treating OCD in our sample. Brown University also conducts a similar study and their outcomes will soon be available. We will discuss factors that might explain these findings, like symptoms severity, functional status, response criteria and treatment planning/radiobiology of radiosurgery lesions.
Supported By: FAPESP (Foundation for the Support of Research in the State of São Paulo)
Keywords: Psychiatric Neurosurgery, Obsessive Compulsive Disorder (OCD), Efficacy, Safety, Prospective Cohort

F37. Interest in Augmenting Standard Treatments of Post-Traumatic Stress Disorder With Spiritually Oriented Therapy Among Veterans

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Background: one third of veterans do not respond to current therapeutics for PTSD. Adjunctive Spiritually Oriented Therapy (SOT) may be important in resolving MI along with PTSD symptoms. Objective: (1) to determine the percentage of veterans who are interested in SOT for PTSD, (2) characterize the similarities and differences between these two groups with respect to demographic and clinical characteristics.
Methods: A survey was completed by 120 veterans enrolled at the Charlie Norwood VA Medical Center, Augusta, Georgia. Demographics and combat information was collected. Standard survey measures were used to determine PTSD severity and religious involvement. Logistic regression models were used to examine the association of demographic, combat, PTSD severity, and religious involvement on a veteran interest in SOT.
Results: Marital status, religious affiliation, and religious involvement were significantly associated with veteran interest in SOT. Married veterans (aOR=0.11, 95% CI=0.03-0.47) were less likely to be interested compared to single people. Veterans with no religious affiliation, or who were agnostic, or atheist (aOR=4.70; 95% CI=1.16-19.12) were more likely to be interested in SOT compared to veterans with a religious affiliation. In addition, veterans with more religious involvement (aOR=1.03; 95% CI=1.01-1.06) were more likely to be interested in SOT.
Conclusions: Those with religious affiliation but less religious involvement were the least interested in SOT. However, veterans with no religious affiliation, or who are agnostic or atheist were interested in in SOT. Additionally, those with higher levels of religious involvement were also interested in in SOT. These findings warrant replication.
Supported By: Augusta Biomedical Research Institute
Keywords: Post-Traumatic Stress Disorder, Veterans, Moral Injury, Spirituality

F38. Forecasting the Course of Post-Traumatic Stress Following Emergency Room Admission: A Machine Learning Approach

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Background: Previous studies identified distinct trajectories of Post-Traumatic Stress Disorder. These studies typically focus on sociodemographic information and severity of potential traumatic brain injury. Moreover, they often investigate these potential predictive factors a long time after the traumatic event took place, thereby limiting the possibility to discern what is a risk factor and what is the consequence of the psychopathology. Thus, there is need to include data comprehensively and to do so immediately after the potentially traumatic event. We examined a broad range of variables in n=338 patients after Emergency Room admission after having experienced a traumatic event. The current work utilizes machine learning to predict post-traumatic stress responses based on biological indicators garnered from electronic medical records including immune markers, heart rate, pulse, along with inter-related endocrine and genetic markers.
Methods: Heterogeneous trajectories of response through 12 months post-trauma will be identified using Latent Growth Mixture Modeling and individuals will be assigned to trajectories based on their most likely class membership by using regularization methods such as Elastic Net for Machine Learning.
Results: A large set of wide data ($p>>n$) consisting of $p>2.000$ variables of n=338 Emergency Room patients (34.9% female and 65.1% male; mean age 37.21 $\pm$ 13.37) has been collected and heterogeneous trajectories have been identified.
Conclusions: The present work demonstrates the potential to identify individuals at risk for abnormal post-traumatic stress responses in emergency medical settings based on accessible, and often readily available sources of information. This introduces the possibility of building algorithms into emergency medical systems to make predictions.
Supported By: Deutsche Forschungsgemeinschaft (DFG): SCHU 3259/1-1, project number: 387444691
Keywords: Post-traumatic Stress Disorder, Machine Learning, Trajectories, Predictors, Emergency Room

F39. Sleep Architectural Correlates of Subjective and Objective Measures of Hyperarousal

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Background: Traumatic-stress disorders are associated with hyperarousal and impaired habituation to salient stimuli. Among trauma-exposed individuals showing a wide spectrum of post-traumatic symptoms, we sought to identify sleep architectural correlates of subjective and objective measures of hyperarousal.
Methods: Fifty participants (ages 18-40, 21 with current PTSD diagnosis) who had experienced a criterion-A trauma within two years completed the Hypervigilance items of the Clinician Administered PTSD scale (CAPS) and PTSD Checklist (PCL-5), the Hyperarousal (HAS) and Hypervigilance (HVQ) scales, the SCL-90, and the Depression Anxiety and Stress Scale (DASS). Participants underwent an auditory startle paradigm in which skin conductance (SCR), blink startle (EMG), and heart rate acceleration (HRA) responses to 16 loud (102dB) tones (1000Hz) were obtained. Mean SCR, EMG, and HRA were computed and their habituation estimated from the slope of responses to successive presentations. Following an acclimation night, ambulatory polysomnography provided sleep-stage percentages (N1-3, REM) and REM latency (REML). Separate stepwise multiple regressions used 10 self-report arousal/anxiety measures and 6 psychophysiological measures to predict each sleep parameter.
Results: Summed CAPS/PCL "sleep difficulty" items predicted higher N1% ($p<0.001$) and REM% ($p=0.036$). CAPS/PCL "difficulty concentrating" predicted lower N1% ($p<0.001$). Hypervigilance predicted lower N2% ($p=0.002$) and CAPS/PCL "recklessness" predicted higher N3% ($p=0.033$). None of the psychophysiological startle responses predicted any of the sleep architecture parameters.
Conclusions: Perceived sleep difficulty predicted elevated percentages of both N1 and REM, perhaps reflecting the heightened arousal in these sleep stages. Hypervigilance may lighten NREM, resulting in lowered N2%. Surprisingly, however, none of the objective psychophysiological measures predicted sleep architecture.
Supported By: 1R21MH101567
Keywords: REM Sleep, PTSD - Posttraumatic Stress Disorder, Hyperarousal, Sleep, Psychophysiology

F40. In Trauma-Exposed individuals, Self-Reported Hyperarousal Predicts Resting-State Functional Connectivity in Frontocortical and Paralimbic Regions

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Background: Traumatic-stress disorders are associated with CNS hyperarousal and impaired emotion regulation. In trauma-exposed individuals having symptoms that varied from absent to sufficient for PTSD diagnosis, we used resting-state functional connectivity (rsFC) to examine associations between self-reported hyperarousal and rsFC anterior salience and executive control networks.
Methods: Forty-two trauma-exposed participants (18-40y, mean=22.8±4.6y) completed psychological interviews that included the Clinician-Administered PTSD Scale (CAPS). A canonical self-report Hyperarousal Scale combined a published hyperarousal scale with the hyperarousal items of the PTSD Checklist and CAPS. Subjects underwent resting-state scans at 3T followed by seed-based rsFC analyses. Seeds were created for 5 fear-related regions – left and right amygdala, left and right anterior insular cortex (AIC), dorsal anterior cingulate cortex (dACC) – and 1 fear-regulatory region – ventromedial prefrontal cortex (vmPFC). Hyperarousal scores were used to predict connectivity between these seeds and regions within a frontocortical and limbic mask.
Results: Hyperarousal scores positively correlated with connectivity between: 1) left amygdala and right primary motor cortex; 2) right amygdala and pons; 3) right AIC and right superior medial frontal cortex; and 4) vmPFC and both supplementary motor cortex and right dorsolateral prefrontal cortex (dlPFC). Hyperarousal scores were negatively correlated with connectivity between: 1) left amygdala and right caudate body; 2) dACC and both left dlPFC and right thalamus; and 3) right AIC and both the vmPFC and right superior frontal cortex.
Conclusions: Among trauma-exposed individuals, hyperarousal predicted variation in connectivity of fear-and emotion-regulatory seeds with motor, frontal association and subcortical regions of the salience, executive control and motor networks.
Supported By: R01MH109638, NIMH
Keywords: Trauma, Resting State fMRI, RDoC, Hyperarousal

F41. Preconception Omega-3 Fatty Acid Deficiency Reduces Maternal Nurturing in Rats

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Background: Young females with mood disorders and of childbearing potential exhibit significant deficits in blood long-chain omega-3 (LCn-3) fatty acids. However, the effects of n-3 fatty acid deficiency on maternal nurturing behaviors are not known. This study investigated the effects preconception n-3 fatty acid deficiency on maternal behavior in rats.
Methods: Female rats (P56) were maintained on a diet with no n-3 fatty acids or a control diet fortified with alpha-linolenic acid for 30 days prior to breeding through to weaning. At P2 litters were culled to n=8 per mother and maternal behavior was video recorded on P3, P6, and P9. Maternal behaviors, included licking and grooming, arched back nursing, blanket nursing, passive nursing, and being off the pups, were quantified in a blinded manner by a trained rater.
Results: Females maintained on the n-3 free diet showed significantly less arched back and blanket nursing at P3, P6, and P9 ($p<0.001$), and less licking/grooming at P3 ($p<0.001$), compared with controls. Passive nursing was significantly greater in n-3 free females at P3 and P6 ($p< 0.001$), and the time off pups was significantly greater in the n-3 free females at P3 and P6 ($p<0.001$).
Conclusions: These findings suggest that moderate dietary n-3 fatty acid deficiency significantly reduces maternal nurturing behavior in rats. The negative impact of n-3 fatty acid deficiency on maternal nurturing behavior may contribute to enduring behavioral and neurochemical abnormalities

observed in offspring of n-3 fatty acid rats, and may represent a mechanism by which these abnormalities are transmitted across generations.
Supported By: This work was supported in part by National Institute of Health grant MH107378 to R.K.M.
Keywords: Maternal, Omega-3 Fatty Acids, Maternal Care

F42. Voluntary Exercise in Rat Dams During Pregnancy Mitigates Cognitive Deficits in Offspring Exposed to Perinatal High Fat Diet

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Background: 1 in 5 women of reproductive age are predicted to be obese by 2025, with many more exposed to the globalized high-fat (HF) "Western" diet. Obesity and overnutrition are associated with cognitive impairment. We previously found that exposure to maternal HF diet (60% kcal fat) during pregnancy and lactation leads to cognitive impairment in rat offspring despite their being weaning onto a low-fat chow diet (CH, 13% kcal fat). Exercise has been shown to improve cognition in humans and rodents, but few studies have assessed the effects of dam exercise during pregnancy on offspring cognition, especially in the setting of maternal HF diet.
Methods: Pregnant Sprague-Dawley rats were divided into 4 groups on day 2 of gestation: CH-Sedentary (CH-SED, n=12), CH-Running-Wheel (CH-RW, n=12), HF-SED (n=11), and HF-RW (n=10). CH or HF was provided ad libitum during pregnancy and lactation, and voluntary exercise via RW during pregnancy only. On postnatal day (P)21, all offspring were weaned onto CH. On P80, male and female offspring's cognitive behavior was tested via the Novel Object Recognition Test and Barnes Maze.
Results: Male and female HF-SED offspring exhibited significantly impaired recognition and spatial memory compared to CH controls. These deficits were not seen in HF-RW offspring, which performed similarly to CH offspring in both behavioral assays.
Conclusions: Our results suggest that voluntary dam exercise during gestation mitigates cognitive impairment in rat offspring exposed to perinatal maternal HF diet and may be a promising and clinically translatable intervention.
Supported By: NIH NIMH
Keywords: DOHaD, Gestational Exercise Exposure, Maternal High Fat Diet, Cognitive Deficits, Rat Model

F43. Lie Detection: How Autistic Traits Impact the Ability to Control Competing Representations of the Self and Others' Opinions

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Background: Autism Spectrum Disorder (ASD) is increasingly considered as a disorder of top-down control or modulation of social behaviour. One candidate mechanism is the control of competing representations of the 'self' and the 'other', coined 'self-other control'. However, cognitive experimental investigation of this mechanism, particularly across social domains in ASD are limited.
Methods: In the present study, 60 participants (22 with ASD) completed a newly developed lie detection task as an index of self-other control (Sowden et al., 2015), probing its relationship with autistic traits (measured by the Autism Spectrum Quotient; AQ). Participants' opinions on a number of topics were first obtained, after which they judged the veracity of other people's opinion statements.
Results: Self-other consistency effects on this task are indicative of a poorer ability to detect truths and lies when the opinions of the self and the other are inconsistent, than when consistent, with one another: the self-opinion must be inhibited, and the opinion of the other person enhanced, for successful performance. Increased AQ scores were significantly related to increased self-other consistency effects ($r = .434$, $p = .001$).
Conclusions: In conclusion, increased autistic traits are associated with an impaired ability to control the competing representations of the opinions of the self and other. This study is the first to demonstrate this using a novel task to index self-other control in relation to opinions and lie detection.
Supported By: Medical Research Council
Keywords: Autism Spectrum Disorder, Self-other Control, Lie Detection

F44. Age-Related Changes in Reversal Learning and Medial Temporal Lobe Circuitry in Children

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Background: The ability to flexibly respond to changes in the environment is critical for adaptive behavior. Reversal learning is a form of associative learning that tests the ability of an organism to change responses when contingencies are altered. For example, conditions that were once rewarding may become threatening and vice versa. Here, we test how reversal learning ability changes with age in a sample of children.
Methods: 39 children (ages 6-12) completed a reversal learning task that involved learning cue+context (e.g., hat on orange background) —>outcome (e.g., coins) associations, and later viewing new associations, which required reversing the outcome of either the cue (e.g. phone on orange background—>bomb) or the context (e.g., hat on gray background—>bomb). Behavioral responses were recorded.
Results: Accuracy during the learning phase improved with age for both positive and negative associations. During the reversal learning phase, there were age-related increases in accuracy for context but not cue reversal trials. When split by valence, there was an age-related increase in accuracy for reversal of negative–>positive contexts, but not positive–>negative contexts.
Conclusions: Our results suggest developmental changes in reversal ability across childhood. Increased reversal ability for

rewarding contexts may correspond with increases in risk taking behavior during the transition into adolescence.
Keywords: Hippocampus, fMRI, reversal learning, development

F45. Interaction Between Childhood Abuse and rs1360780 of the FKBP5 Gene on Amygdala Resting State Functional Connectivity in Young Adults

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Background: Childhood adversity has been identified as an important factor in the development of stress-related mental disorders, while rs1360780 of the FKBP5 gene was found related to influence hypothalamic-pituitary-adrenal (HPA)-axis function. Here, we tested whether childhood adversity and rs1360780 interact on amygdala subregion resting-state functional connectivity (rsFC).
Methods: rsFC MRI data were acquired from 573 healthy 18-year-old subjects of the longitudinal IMAGEN sample. Childhood abuse was assessed using the Childhood Trauma Questionnaire (CTQ). rs1360780 was genotyped using IMAGEN genetics protocols. Interaction effects for a history of childhood abuse (yes vs. no) and genotype (TT vs. CT/CC) on left and right centromedial and basolateral amygdala connectivity were tested using seed-based connectivity analyses, masking for areas of the salience network (insula and anterior cingulate) and controlling for grey matter volume.
Results: An interaction between childhood abuse and genotype in rsFC of the right centromedial amygdala was found in the right posterior insula and left dACC ($p<.05$, FWE corrected). The interaction was driven by increased amygdala rsFC in TT-carriers with childhood abuse as compared to CT/CC-carriers. Inclusion of grey matter volume as covariate did not change the results.
Conclusions: Our results suggest that amygdala rsFC increases with regions of the salience network may be a functional correlate of a dysregulated HPA-axis after childhood abuse in TT-risk allele carriers. As such, this gene-environment interaction may relate to an enhanced risk for developing stress-related disorders. These findings may ultimately contribute to better individual risk assessments after trauma.
Supported By: BMBF, Germany
Keywords: FKBP5, Amygdala, Resting State Functional Connectivity, Gene-Environment Interaction, Childhood Trauma

F46. Brain MRI Morphometry Changes Associated With Na+/H+ Exchanger 6 (NHE6) Mutations in Christianson Syndrome (CS)

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Background: Single gene disorders replicating aspects of otherwise heterogeneous neuropsychiatric conditions may help model relevant pathophysiologic mechanisms. CS, caused by mutations in X-linked NHE6, a major regulator of endosomal pH, is one such illness characterized by neurodevelopmental abnormalities including autism, cognitive disability, and neurodegenerative pathology. NHE6 mutations may, therefore, offer insight into the role of disrupted endosomal protein trafficking in neuropsychiatric disease. Here, we discern how NHE6 mutations impact human brain morphology focusing on corpus callosum (CC) and cerebellum, structures intensely studied in autism.
Methods: 24 T1-weighted midsagittal clinical MRIs from 13 males, ages 0.6-11 years, were identified from the International CS and NHE6 (SLC9A6) gene study network. Measures of brain regions including CC and cerebellum were collected and compared to age-matched reference data using repeated measures one-way ANOVA or between individual subjects at different time points using regression analysis.
Results: Fronto-occipital diameter (FOD) of brains of CS individuals was significantly smaller than median age-matched reference data ($p=0.0001$), while most CC measures including antero-posterior diameter of CC/FOD were significantly greater than the median ($p=0.0001$). Additionally, we discerned several MRI signatures of cerebellar disease that may prove useful for diagnostic recognition of CS.
Conclusions: In CS, cerebellar atrophy shows distinctive features, which may serve for diagnostic purposes. Further, CC is larger than expected. The reason for this is unclear, but overgrowth seems unlikely, as megaloencephaly is usually seen in other mega-CC syndromes. Instead, abnormal endosomal trafficking leading to protein accumulation and axonal hypertrophy seems more likely and will be explored further in CS mouse model.
Supported By: Hassenfeld Child Health Innovation Institute
Keywords: Christianson Syndrome, Na+/H+ Exchanger 6 (NHE6), Corpus Callosum, Cerebellum, MRI Brain Imaging

F47. Infant Telomere Length Differs in Matched and Mismatched Postnatal Expectancy

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Background: The deleterious effects of maternal adverse childhood events (ACE) and prenatal stress (PNMS) are established and these experiences are likely biologically embedded in the infant. The Mismatch hypothesis of the Developmental Origins of Health and Disease model suggests that differential fetal development occurs based on expected postnatal exposures and that adaptation to environmental changes is costly. One marker of biological cost, linked to both transgenerational adversity and PNMS, is telomere length (TL). This study examined the Mismatch hypothesis on infant TL.
Methods: This study included 114 mother-infant dyads and demographic, maternal ACE, and PNMS data were collected

prenatally. Infant TL was assessed by MMqPCR from newborn bloodspots and buccal swabs at 4, 12, and 18 months of age. Infants were categorized as matched if mothers reported either high ACE and high PNMS or low ACE and low PNMS. Mismatched infants had mothers with alternate combinations. T-tests assessed the relation with newborn TL and multi-level mixed-effects models assessed the effects on infant TL across the first 18 months of age.
Results: Matched infants (n=67) exhibited greater newborn TL relative to mismatched infants (n=47) (t=-2.09; p=0.039). Matched infants exhibited greater TL across all time-points than mismatched infants (β=0.19; p=0.009). Accounting for covariates attenuated the effect, however findings remained significant (β=0.17; p=0.02).
Conclusions: These findings highlight the need to consider maternal preconception adversity in tandem with PNMS when examining both biological outcomes and health trajectories. Understanding these pathways is necessary to design effective interventions to address multi-generational impacts of early life adversity.
Supported By: NIH: 1R01MH101533-01, 3R01MH101533-02S3
Keywords: Telomere Length, Adverse Childhood Experiences, Prenatal Maternal Stress, Longitudinal Study, Intergenerational Transmission

F48. Epigenetic Markers of the Intergenerational Transmission of Stress

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Background: Recent studies have shown that stress experienced by mothers during pregnancy or earlier in life, can be transmitted to next generations, indicated by enhanced vulnerability to stress-related disorders in their offspring. The routes via which this intergenerational transmission of stress occurs are still to be elucidated. We examined possible epigenetic markers of the association between mothers' childhood traumatic experiences and their offspring's stress reactivity.
Methods: The Dutch BIBO cohort includes 173 mother-infant pairs followed since pregnancy. At age 6, 148 children were subjected to a social stress test, during which cortisol reactivity was measured. Their buccal tissue was analysed with the 850k EPIC Illumina array. Maternal childhood trauma was examined via self-report.
Results: Mothers' childhood trauma was significantly associated with child cortisol reactivity ($r = .19$, $p < .05$). An EWAS was performed on child cortisol reactivity. More than 50 CpGs showed significant associations at an FDR .2 level. These CpGs were then examined in relation to maternal trauma scores, with 1 CpG on chromosome 17 showing a strong, significant association ($p = .001$). Methylation in this CpG site statistically mediates the association between maternal childhood trauma and child cortisol reactivity. It is located in an inter-genic region, with a number of transcription factor binding sites nearby, including for NR3C1.
Conclusions: We found an epigenetic marker for the association between maternal childhood trauma and offspring stress reactivity. This association was not due to differences in postnatal care, indicating that the transmission of early life stress from mother to child may be mediated by epigenetic mechanisms.
Supported By: Netherlands Organisation for Scientific Research (NWO); Sackler Program for Epigenetics and Psychobiology; CIFAR Child and Brain Development: Douglas Mental Health University Institute; Leiden University
Keywords: Epigenetics, DNA methylation, Childhood Trauma, Cortisol Reactivity, Early Life Stress

F49. Genetic Basis of Changes in Neurocognition and Psychopathology Between Childhood and Adulthood

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Background: Identifying genes associated with changes in neurocognition and psychopathology will advance understanding of the biological mechanisms underlying normal and abnormal development.
Methods: Using data from the Philadelphia Neurodevelopmental Cohort (PNC), a general population sample ($n = 6638$), we examined genetic influences on changes in neurocognition (executive function, memory, reasoning, social cognition, speed and general cognition) and psychopathological dimensions (psychosis, anxious-misery, externalizing and fear) between childhood and adulthood (8–21 years). We applied an advanced quantitative gene-by-environment interaction analysis, with age modeled as an environmental factor, to examine the genetic basis of these changes with increasing age. Decomposing gene-by-age ($G \times A$) interactions enabled testing of whether these genetic effects are due to 1) fluctuations in action of the same genes over time, or 2) to variation in the genes themselves over time.
Results: We found profound changes in neurocognition and psychopathological dimensions between childhood and adulthood. Small to moderate negative correlations were observed between neurocognitive domains and psychopathological dimensions. Genetic influences on changes in neurocognitive and psychopathological scores were substantial (20-71%). Furthermore, by decomposing gene-by-age ($G \times A$) interactions, we inferred that these changes as a function of age were due to both fluctuations in action of the same genes, as well as variation in the genes themselves.
Conclusions: These results demonstrate that neurocognitive and psychopathological traits sensitive to genetic influences on development can be identified, a critical first step in

delineating the biological mechanisms underlying normal and abnormal development.
Supported By: RO1
Keywords: Genetics, Cognitive Development, Developmental Psychopathology

F50. Genetic Architecture of Hippocampal Subfield Volumes: Shared and Specific Influences

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Background: The hippocampus is a heterogeneous structure, comprising histologically distinguishable subfields. These subfields are known to be differentially involved in memory consolidation, spatial navigation and pattern separation, complex functions often found to be impaired in individuals with brain disorders associated with reduced hippocampal volume, including Alzheimer's disease (AD) and schizophrenia. Given these structural and functional differences, we sought to characterize the subfields' shared and specific genetic architecture.
Methods: T1-images (n= 17418, 16 cohorts) were processed with the hippocampal subfields algorithm in FreeSurfer v6.0. We calculated the SNP-based heritability of 12 subfields, as well as their genetic correlation with each other, with other structural brain features, and with AD and schizophrenia. We further ran a genome-wide association analysis on each subfield, correcting for total hippocampal volume. All analyses included age, age2, sex, and intracranial volume as covariates.
Results: Volumes of all subfields were heritable (h2 ranging from .15 to .29, all $p < 2.2 * 10\text{-}9$) and clustered together (genetic correlations Rg>.41), compared to other brain features. The subiculum and the hippocampal-amygdalar transition area (HATA) showed significant genetic correlation with AD and schizophrenia, respectively. We found 14 independent whole-genome significant loci across six subfields, of which eight had not been previously linked to the hippocampus. Top SNPs were annotated to genes associated with neuronal differentiation, locomotor behaviour, schizophrenia and AD.
Conclusions: Hippocampal subfields have partly distinct genetic determinants, associated with specific biological processes and traits. Taking into account this specificity may aid in furthering our understanding of hippocampal neurobiology and associated disorders.
Keywords: Hippocampal Subfields, Brain Volumes, Genome-Wide Association Study, Genetic Correlation, Schizophrenia

F51. Investigating the Effect of Glutamate on Executive Functions in Children with Attention-Deficit/Hyperactivity Disorder Using Magnetic Resonance Spectroscopy

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Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder in children, with a prevalence of 5-7%. Symptoms include inattention, impulsivity and hyperactivity. Previous studies have reported dysfunction in the glutamatergic pathway. However, no studies to date have linked the glutamate differences with performance in Executive Function (EF) tasks.
Methods: 31 children with ADHD (M = 10.2 years, SD = 1.3; males = 19) and 15 control participants (HC; M = 10.0 years, SD = 1.4 years; males = 6) took part. Short echo proton magnetic resonance spectroscopy (1H-MRS; TE = 30ms) were used to study the changes in in the right prefrontal cortex (R-PFC) and left striatum (LS). Both groups completed an EF assessment battery, Digit Span (DSB), Letter Fluency (LF) and Trail Making Test—Part B, (TMT-B).
Results: Independent t-tests found lower concentrations of Glutamate (Glu; p = 0.009), Choline (Cho; p = 0.016) and N-Acetyl Aspartate (NAA; p = 0.029) in the R-PFC in ADHD participants compared to HC. No significant differences were seen in the LS. Positive correlation with Glu concentration and performance in DSB, LF and TMTB tasks in the control group were observed. No such correlations were observed in the ADHD group.
Conclusions: To our knowledge, this is the first study to investigate the relationship between EF and Glu concentration. These findings suggest the decoupling effect of Glu in EF related tasks in children with ADHD compared to controls. As such, Glu concentration can be a possible ADHD biomarker and the RPFC can be a novel treatment target for future.
Supported By: Alberta Children's Hospital Foundation
Keywords: ADHD, Magnetic Resonance Spectroscopy, Glutamate, Executive Function

F52. Age-Associated Functional Network Organization in Psychosis

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Background: Psychotic symptoms are believed to result from aberrant integration of information processing between coordinated brain networks. It is unknown whether these networks are intact or disrupted during development from adolescence through adulthood in psychosis spectrum youth.
Methods: Resting state functional neuroimaging (rsfMRI) data were collected on 678 participants (typically developing=516; psychosis spectrum=164, ages 10-25 years) from the Philadelphia Neurodevelopmental Cohort (PNC) and a longitudinal cohort of typically developing youth (LUNA). We extracted individual time series from an established rsfMRI parcellation and calculated correlations among the parcellation regions. Group averages were calculated in four age groups (late childhood, early adolescence, late adolescence, adulthood). We implemented the Louvain community detection algorithm and a clustering comparison technique, Normalized Mutual Information, to compare identified network organization to the established rsfMRI parcellation. We used jack-knifing and permutation testing to assess stability across four age groups in typically developing youth from the PNC and Luna and psychosis spectrum youth from the PNC. Finally, we compared the stability of network organization between controls and psychosis spectrum youth.
Results: Network organization was stable across the four age groups in the PNC typically developing youth (all $p>0.2$), LUNA (all $p>.2$), and PNC psychosis spectrum youth (all $p>0.15$). Psychosis spectrum youth had similar functional network organization in comparison to typically developing youth during all developmental stages (all $p>0.67$).
Conclusions: Gross functional network organization is stable in typically developing youth and psychosis spectrum youth. Future analyses will examine to what extent other aspects of connectivity for resting state networks are altered across development.
Supported By: R01 MH080243; R21 HD074850; K01 MH112774
Keywords: Adolescence, Brain Networks, Resting State fMRI, Psychosis Spectrum

F53. Outward Subcortical Deformations Associated With Sub-Clinical Depression Symptoms in Adolescents

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Background: Many studies report morphological alterations of subcortical regions in individuals with mood disorders, however inconsistencies in the literature exist, with some reporting increases in volume. These discrepancies are potentially due to age, unrepresentative samples, illness state, medication confounds, or coarse measurements of volume. We undertook a more sensitive shape analysis in a large representative sample of adolescents with subclinical levels of depression.
Methods: We conducted FreeSurfer-initiated Large Deformation Diffeomorphic Metric Mapping (FS+LDDMM) of subcortical structures using structural 3T MRI in 256 teenagers (mean age=14) stratified for gender, ethnicity and family socioeconomic status (SES). Surfstat implemented in MATLAB regressed morphometric changes on T scores (accounting for gender and grade) from the Depression scale of the Revised Children's Anxiety and Depression scale (RCADS). Age, gender, Caucasian race, puberty status, intracranial volume and SES were covaried. Multiple comparisons correction was performed using Random Field Theory FWE ($p< .05$).
Results: Depression (M=46.98, SD=10.14) scores were primarily subclinical (only 3.12% of participants scored above clinical threshold) and did not correlate with volume of any structure. However, higher depression scores predicted more outward shape deformity in the left hippocampus (subiculum and CA1), amygdala, nucleus accumbens, caudate, putamen and thalamus.
Conclusions: This is the first study to report regional outward deformity in multiple left hemisphere subcortical structures associated with adolescent's subclinical depression symptoms. Consistent with suggestions that subcortical morphometric changes in depression are state-dependent; these results may reflect compensatory plasticity. Alternatively, they could reflect accelerated maturation of subcortical structures associated with depression symptoms.
Supported By: 1 R01 HL122328 NHLBI/NICHD (PI: Miller)
Keywords: Socioeconomic Status, Surface-based Morphometry, Adolescent Depression

F54. Methylation of the Dopamine Transporter Gene in Blood is Associated With Striatal Dopamine Transporter Availability in ADHD

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Background: Dopamine transporters (DAT) are implicated in the pathogenesis and treatment of attention deficit hyperactivity disorder (ADHD) and are upregulated by chronic treatment with methylphenidate, the commonly prescribed medication for ADHD. Methylation of the DAT1 gene in brain and blood has been associated with DAT expression in the brain of rodents. However, the associations in human are still unclear.
Methods: We tested the association between methylation of the DAT1 promoter derived from blood and DAT availability in the striatum of unmedicated ADHD adult participants (n=13) and in that of healthy age-matched controls

(HC; n=34) using Positron Emission Tomography (PET) and [11C] Cocaine.
Results: Results showed that there were no between-group differences in DAT1 promoter methylation or striatal DAT availability. However, the degree of methylation in the promoter region of DAT1 correlated negatively with DAT availability in caudate, putamen, and ventral striatum (VS) in ADHD participants only. DAT availability in VS correlated with inattention scores in ADHD participants. We verified in a postmortem cohort (n=8 with ADHD diagnosis, n=22 without psychiatric diagnoses) that DAT1 promoter methylation in peripheral blood correlated positively with DAT1 promoter methylation extracted from substantia nigra (SN) in both groups. DAT1 gene expression in SN further correlated positively with DAT protein expression in caudate.
Conclusions: These findings suggest that peripheral DAT1 promoter methylation may be predictive of striatal DAT availability in adults with ADHD. Methylation of DAT1 in blood may therefore be a relevant biomarker for DAT expression in the brain of individuals with ADHD.
Supported By: Y1AA-3009
Keywords: ADHD, Dopamine Transporter, DNA Methylation, Caudate

F55. Recent Use of Internet Associates With Increase in Brain Resting-State Modularity in a Community Sample of Children and Adolescents

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Background: The effect of the increasing use of the internet on youth's brain remains unclear. Higher resting-state brain modularity, a measure on how subnetworks are embedded within a larger network, favors performance in simple tasks, whereas lower modularity favors performance in complex tasks. Internet most popular uses are low-demanding and highly reinforcing. Whether this affect brain modularity was not explored yet.
Methods: Three-hundred seventy-four participants, with mean age of 14.39 years (sd 1.85), and 58.28% male, underwent functional magnetic resonance scanning in two cities. They reported internet use on the previous day (recent use), the use length in hours, and similar questions about their use on the last six months (prolonged use). BOLD-signal correlation matrices between brain modules was calculated to assess modularity. Analysis were controlled for age, gender, head movement, acquisition site, diagnostic, socioeconomic status, ethnicity and parental education level.
Results: Brain modularity was higher amongst those participants who used the internet on the previous day ($df = 1$, $F = 20.791$, $p = 7.17x10$). Brain modularity also differed across length of use categories ($df = 3$, $F = 2.912$, $p = 0.0348$), but not linearly. Modularity did not correlate with variables about the last 6 months use ($df = 4$, $F = 1.119$, $p = 0.35$).
Conclusions: Our results reinforce the need of investigating internet use impact on the developing brain. Recent use of internet, rather than prolonged use, affected brain modularity. We expect that the 3-year follow-up of our sample can better inform on the association direction.
Keywords: Internet, BOLD Functional MRI, Neural Networks

F56. Fluctuating and Emerging Genetic Influences on Cortical Development During Adolescence

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Background: Cortical thickness (CT) is under strong genetic control across the life span. However, there are individual differences in the developmental trajectory of cortical development and thus far the genetic influences that cause changes in cortical thickness (ΔCT) during brain development have not been studied much.
Methods: We obtained 482 longitudinal MRI scans at ages 9, 12, and 17 years from 215 twins (from 47 MZ and 62 DZ twin pairs) and applied genetic structural equation modelling to estimate genetic correlations for (1) cortical thickness between regions and across time, and (2) the genetic underpinnings of changes in cortical thickness over time.
Results: Cortical thickness is largely influenced by the same genetic factor throughout late childhood and adolescence, but we also found evidence for different genetic factors across space and time. Specifically, clustering of the genetic correlation matrix separates the frontal, parietal, and temporal lobes at age 17 years from ages 9 and 12 years. The extent to which cortical thinning occurs is also under genetic control during adolescence: this is mostly due to fluctuations in the importance of the influence of the same genetic factor, with locally evidence of additional genetic factors.
Conclusions: These fluctuating core and emerging genetic factors influencing cortical thickness might contribute to the rapid cognitive and behavioural development during childhood and adolescence, and could potentially be targets for investigation of the manifestation of psychiatric disorders that have their origin in childhood and adolescence.
Supported By: NWO; NWOMagW; NWO-NIHC; NWO/SPI; ERC; Utrecht University
Keywords: Developmental Trajectories, Cortical Thickness, Heritability, Twins

F57. Shorter Sleep Duration is Associated With Lower Frontolimbic Connectivity in Children

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Background: Adequate sleep is essential for cognitive and emotional functioning, and 8 to 12 hours of sleep is recommended for school-age children and adolescents. However, national survey data indicate that sleep duration declines from 8.5 hours to 7.2 hours from ages 13 to 18. Given that shorter

sleep duration has been associated with poorer emotion regulation ability, the present study tests the hypothesis that shorter sleep duration will be associated with lower next-day functional connectivity (FC) between the amygdala and medial prefrontal cortex (mPFC), a key frontolimbic circuitry involved in the regulation of emotion.
Methods: 63 children and adolescents (6-17 years, 34 females) completed a sleep journal and were scanned the next day using resting-state functional magnetic resonance imaging. FC of the amygdala was computed, and effects of sleep duration on amygdala FC was estimated using whole-brain regression analyses.
Results: Shorter sleep duration was associated with lower FC between the left amygdala and the mPFC, as well as the orbitofrontal cortex and the adjacent pregenual cingulate cortex. Like the mPFC, these areas are implicated in emotion regulation. Conversely, shorter sleep duration was associated with higher FC between the amygdala and the thalamus, anterior insula, and dorsal/middle anterior cingulate cortex - areas associated with emotional expression and reactivity.
Conclusions: Together, these results suggest that sleep duration is associated with next-day FC within emotion-related neural circuitry in children and adolescents. Our results suggest that shorter sleep duration may be associated with both greater emotional reactivity and poorer control over emotional responding.
Supported By: American Cancer Society; National Institute of Mental Health
Keywords: Sleep Duration, Children and Adolescence, Fronto-limbic Connectivity, fMRI Resting State, Amygdala

F58. Low-Dose Penicillin Exposure in Adolescent Mice Leads to Long-Term Deficits in Social Odour Recognition: Implications for Microbiota & Olfaction in Disorders Involving Social Communication

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Background: Recent work has demonstrated that low-dose penicillin treatment of mice during pre- and early post-natal periods has long-term effects on offspring behavior, brain neurochemistry and microbiome (Leclercq et al 2017), many of which are prevented by concurrent treatment with a probiotic. We have now observed that low-dose penicillin during adolescence results in long-term behavioural change. Adolescence is a vulnerable period in brain development, and a time in humans when psychiatric illness often first manifests. While processing of olfactory cues is recognized as integral to rodent behavior, this is often neglected in such studies. We therefore examined the impact of low-dose penicillin treatment during adolescence on social odour discrimination.
Methods: 3-week-old weanling Balb/c mice were randomized into treatment groups of water (control), low-dose penicillin (AB = 31 mg/kg penicillin V in drinking water from 18:00-9:00/day) or AB plus Lactobacillus rhamnosus JB-1TM (109 c.f.u./day) in drinking water from 9:00-18:00 (AB/JB-1). Treatments continued from 3w to 6w of age. At 10w mice underwent olfactory testing, examining discrimination of both non-social and social odours. Brain, gut, blood and stool were collected post-mortem.
Results: Adolescent low-dose penicillin treatment resulted in long-term olfactory deficits specific to social discrimination, which were attenuated with co-treatment of AB/JB-1. Non-social odour discrimination was unaffected.
Conclusions: Low-dose penicillin treatment during adolescence has long-term effects on social odour discrimination, indicating a role for intestinal microbiota in the etiology of disorders involving social communication. Further, the data suggest that timing of antibiotic treatment may be a target for future clinical research.
Supported By: CIHR/CAG
Keywords: Gut Microbiota, Antibiotic, Olfaction, Social Processing

F59. Altered Corticostriatal Activations and Connectivity During Reinforcement Learning in Unmedicated Adults With Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions) to avoid or reduce distress. Animal and human research suggest that dysfunction in cortico-striato-thalamo-cortical (CSTC) circuits that support reward-based learning may underlie OCD symptoms. Although abnormal functioning of mesolimbic and ventral striatal circuitry during reward-based spatial learning has been documented in OCD, unclear is whether the functioning of CSTC circuits during stimulus-response (S-R) learning is altered or preserved in OCD.
Methods: We used computational fMRI with a reinforcement learning (RL) model to assess striatal activation and CSTC connectivity (i.e., psychophysiological interaction [PPI]) in 28 unmedicated adults with OCD and 28 healthy controls (HC) during their performance of a virtual reality-based task analogous to the "win-stay" version of a radial-arm maze task used in rodents. Whole-brain second-level GLM will be used to assess differences fMRI activation and connectivity associated with stimulus-response (S-R) RL processes across groups.
Results: Both groups engaged right posterolateral striatum with learning, consistent with previous findings from healthy adults ($p<.005$, FWEc). Unlike HCs, OCD participants significantly deactivated bilateral anterior striatum with learning ($p<.005$, FWEc), consistent with previous reports of abnormal recruitment of goal-directed circuitry during reward learning. Exploratory functional connectivity analyses revealed greater learning-related increases in sensorimotor cortico-striatal connectivity in OCD compared to HC participants ($p<.005$, uncorrected).
Conclusions: These findings suggest that, in addition to the well documented deficits in goal-directed learning in OCD, S-R

learning processes may also be abnormal (enhanced), possibly contributing to the habitual nature of the compulsive, ritualistic behaviors that characterize the disorder.
Supported By: NIMH R01MH090062
Keywords: Obsessive Compulsive Disorder (OCD), Reinforcement Learning, Brain Imaging, fMRI, Functional Connectivity, Cortico-Striatal-Thalamic-Cortical Circuit

F60. Changes in Functional Connectivity During Predictive Contextual Processing in Subjects With Asperger's Syndrome

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Background: We investigated the proposition that Autism Spectrum Disorders is associated with task-specific functional connectivity changes.
Methods: We recorded EEG in subjects with Asperger's syndrome (AS) and controls during the performance of a predictive local contextual processing task using abstract stimuli (triangles at different orientations) or emotional faces. Recording blocks consisted of targets preceded by either randomized sequences of standards or by sequences including a three-standard predictive sequence signaling the occurrence of a subsequent target event. We evaluated event-related functional connectivity using synchronization likelihood and graph theoretical analysis.
Results: We observed higher cluster coefficients as well as increases in the local efficiency (in the theta and beta frequency range, respectively) in AS compared to control subjects, indicating increased functional modularity in AS. Importantly, these changes were specific to predicted targets, but were not observed for random targets or standard stimuli. Changes between AS and control subjects were more pronounced during the processing of emotional faces compared to abstract stimuli.
Conclusions: These findings suggest that AS is associated with functional connectivity changes that are specific to the processing of predictive stimuli, and that these changes are more pronounced during the processing of emotional faces.
Supported By: This work was supported by grants from the Spanish Ministry of Science and Innovation (PSI2015-65894-R to N.F), the Ramón y Cajal national fellowship program (to N.F) and by the NSFC (61473062 to L.L).
Keywords: Predictive Local Context, EEG, Functional Connectivity, Asperger's Syndrome

F61. Long-Term Effects of Cognitive Behavioral Therapy on Planning and Prefrontal Cortex Function in Pediatric Obsessive-Compulsive Disorder

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Background: Previous studies showed changes after cognitive behavioral therapy (CBT) in prefrontal cortex function and cognitive performance in pediatric obsessive-compulsive disorder (OCD). It remains unknown whether these changes are short lasting or persistent during a period of brain maturation. Here, we investigated the long-term effects of cognitive behavioral therapy (CBT) on planning performance and brain function in pediatric OCD using a longitudinal design.
Methods: Fifteen pediatric OCD patients and sixteen matched healthy controls ranging from the ages of 8-18 years performed the Tower of London planning task during functional magnetic resonance imaging (fMRI) at three time points; before treatment, after 16 sessions of CBT and after two years of naturalistic follow up.
Results: Group by time interaction analyses showed differential changes from baseline to long-term follow-up in planning performance and brain activity between patients and controls. At baseline, patients were slower but as accurate on the planning task, and recruited the left inferior frontal gyrus, middle frontal gyrus and anterior insula more than controls. These differences were no longer present after CBT and after two years follow-up.
Conclusions: Pediatric OCD patients showed longer reaction times and additional recruitment of frontal brain regions during planning compared with healthy controls. These differences tended to normalize after CBT and the process continued during two years of follow-up. This longitudinal study shows long-lasting changes in cognitive performance and prefrontal cortex function after CBT and suggests that planning dysfunction in pediatric OCD is a state rather than a trait characteristic of the disorder.
Supported By: This study was supported by the University of Amsterdam, the Amsterdam Graduate School for Neuroscience (ONWA), and the Netherlands Organization for Scientific Research (NWO/ZonMW Vidi 016.156.318).
Keywords: Functional MRI, Executive Functioning, Cognitive Behavior Therapy, Prefrontal Cortex, Pediatric OCD

F62. Neonate BDNF Gene Regulation Associates With Maternal Trauma and Fear History

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Background: Exposure to early life trauma associates with consequences across the lifespan and even into the next generation and recent studies have noted the role of BDNF (brain-derived neurotrophic factor) in placental and fetal development. Moreover, evidence suggests maternal early life stress may promote sex-specific intergenerational effects due to prenatal developmental differences. We sought to determine if maternal trauma and fear associated with BDNF DNA methylation and expression in neonates.

Methods: This research data is from the Tennessee CANDLE study, which was designed to examine early child-development risks. Maternal trauma (physical or sexual abuse prior to 18 years) and fear (summary score of perceived fear) were measured using the Traumatic Lifetime Events Questionnaire. DNA methylation and gene expression were measured in umbilical cord blood in 216 mother-child pairs (55.0% African-American; aged 27.0 5.2 years; 49.1% male neonates). Neonates' BDNF methylation and expression were regressed on maternal trauma, controlling clinically relevant covariates including race and cell composition.
Results: Maternal childhood abuse did not associate with BDNF methylation or expression in a combined analysis of both sexes. Maternal childhood abuse predicted increased BDNF expression in male neonates ($p = .001$, $B = .471$). Maternal fear positively associated with DNA methylation of BDNF (cg27351358, exon I) in males ($p = .001$, $B = .004$) but not with expression. Maternal fear negatively associated with BDNF expression in females ($p = .004$, $B = -.12$).
Conclusions: These findings demonstrate a potential for maternal trauma and fear to affect gene regulation in neonates and supports sex-specific analyses of prenatal exposures.
Keywords: Epigenetics, Child Abuse, Intergenerational Transmission

F63. Polygenic Risk: Predicting Depressive Symptoms in Clinical and Epidemiological Cohorts of Adolescents

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Background: With the increase in major depressive disorder (MDD) during puberty, identifying early risk factors in adolescence could have crucial implications for prevention efforts. The current study examined the association of the polygenic risk score (PRS) derived from the recent findings of the Psychiatric Genomics Consortium (PGC) of MDD with clinically important features of depression in a clinical and epidemiological sample of adolescents.
Methods: In the clinical sample, 277 genotyped adolescents with MDD (Mage=15.2(1.98), 68.6% female) and 192 healthy controls (Mage=15.0(2.54), 63.5% female) completed a semi-structured clinical interview and well-established self-report measures of depressive symptoms. The epidemiological cohort was composed of 1,425 genotyped adolescents (Mage=14.0(.92), 63.2% female) who completed self-report measures of depressive symptoms and rumination. PRS were calculated from the imputed genotype dosage using GWAS summary statistics from the most recent PGC-MDD and 23andme findings based on 130,664 MDD cases and 330,470 controls.
Results: In the clinical sample, the PRS of MDD predicted case-control status (log odds=8369.90, se=2254.00, $p<.001$) and severity of depression symptoms ($\beta= 877.28$, se=1214.67, $p=.018$). Among the cases, patients with an earlier onset of depression had higher PRS of MDD than those with a later onset of MDD ($\beta= -6601.95$, se=2847.73, $p=.021$). In the epidemiological cohort, higher PRS of MDD were associated with higher depressive symptoms ($\beta=12617.09$, se=4438.76, $p=.001$) and rumination ($\beta=7518.68$, se=2128.74, $p<.001$).
Conclusions: PRS of MDD in adults generalize to depression in adolescents and may serve as an early indicator of clinically interfering levels of depression in adolescents.
Keywords: Adolescent Depression, Polygenic Risk Score, At-Risk Youth, Biomarkers

F64. The Neuropsychiatric and Behavioral Phenotypes of 3q29 Deletion Syndrome

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Background: 3q29 deletion syndrome (3q29DS) is a rare (~1:30,000) genomic disorder caused by a 1.6 Mb deletion on chromosome 3, and is associated with intellectual disability, anxiety, Autism Spectrum Disorder (ASD), and schizophrenia.
Methods: We used Emory University's 3q29DS registry (3q29deletion.org) to collect data on 88 3q29DS patients, including a custom medical and demographic questionnaire (n=88); Achenbach Behavior Checklists (CBCL/ABCL, n=45); Social Responsiveness Scale (SRS, n=48); and the Social Communication Questionnaire (SCQ, n=30). Statistical testing and data visualization were performed in R.
Results: Self-report data from 3q29DS registry participants shows increased prevalence of ASD diagnosis versus the general population (30.7% vs. 1.47%, $p<2.2e-16$). Scores on the SRS are elevated among all individuals with 3q29DS; 3q29DS patients who do not report an ASD diagnosis scored significantly higher on the SRS (p=2.03e-8), SCQ (p=0.00016), and CBCL/ABCL (p=1.31e-9) as compared to non-ASD, non-3q29DS children. Frequency of ASD diagnosis is similar between 3q29DS males and females, unlike individuals with ASD in the general population.
Conclusions: The 3q29DS population is significantly enriched for ASD diagnosis and ASD features measured via standardized ASD surveys; however, several individuals scored in the clinical range on all scales, despite reporting no diagnosis of ASD. This implies that either ASD is underdiagnosed or not adequately assessed in 3q29DS patients, or additional psychopathology is present that may be independently elevating scores. This finding has implications for both standard of care recommendations for individuals newly diagnosed with 3q29DS, as well as for long-term neuropsychiatric care.
Supported By: RO1; T32;
Keywords: Autism Spectrum Disorder, Anxiety, 3q29 Deletion Syndrome, Genetics, Behavior

F65. Metabolite Abnormalities in the Anterior White Matter of Patients With Pediatric Bipolar Disorder

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Background: Anterior white matter abnormalities have been consistently reported in pediatric bipolar disorder. However, the nature of the metabolites responsible for the functioning of these neural networks in affected bipolar children is poorly understood.
Methods: Using a 3-T MRI scanner and LCModel, measurements from five anatomically distinct voxels in the anterior white matter were acquired for 49 subjects between the ages of 8 and 18 (17 healthy controls, 16 bipolar, and 16 offspring of bipolar parents). Differences in the mean ratios of glycerophosphocholine plus phosphocholine (GPC+PC)/phosphocreatine-creatine (Pcr-Cr) and N-acetylaspartate (NAA)/Pcr-Cr between groups were evaluated with gender and age as covariates.
Results: In two of the left anterior white matter voxels, bipolar children had significantly lower NAA/Pcr-Cr (p=.002; p=.002) and GPC+PC/Pcr-C (p=.006; p=.009) ratios than healthy controls. Ratios of the offspring group were not significantly different than either the bipolar or healthy groups.
Conclusions: NAA is a neuronal marker, and a decrease in NAA/Pcr-Cr can be interpreted as a decrease in neuronal integrity. In addition, choline is vital to the structure of neuronal cell membranes. Hence, the observed decrease in NAA and GPC+PC concentrations in bipolar children implies a molecular mechanism behind frontal lobe pathologies. Future work will examine how these findings relate to microstructural measures derived from diffusion tensor imaging.
Supported By: NIMH grant R01 085667, the Dunn Research Foundation and the Pat Rutherford, Jr. Endowed Chair in Psychiatry (Jair C. Soares).
Keywords: MRS Imaging, Pediatric Bipolar Disorder, Bipolar Offspring

F66. The Effect of Traumatic Brain Injury on Superficial White Matter in Youth: Towards a Personalized Injury Profile

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Background: Diffusion Tensor Imaging (DTI) studies of traumatic brain injury (TBI) have focused on alterations in microstructural features of deep white matter fibers (DWM). Postmortem studies have demonstrated that injured axons are often observed at the gray-white matter interface beneath the cerebral cortex where superficial white matter fibers (SWM) mediate local connectivity between cortical gyri. The objective of this study was to examine if SWM is at increased risk for injury compared to DWM through group-wise and personalized approaches.
Methods: In a community sample of youth (TBI=10, NoTBI=70), we analysed DTI data using a SWM mask and tract-based spatial statistics to identify differences in SWM and DWM fractional anisotropy (FA) between groups with and without a history of TBI. To assess personalized injury profiles the number of abnormal FA clusters was compared between DWM and SWM using subject-specific z-score maps in youth with a history of TBI.
Results: Group wise comparison of DWM and SWM between youth with and without a history of TBI produced no results that survived threshold free clustering enhancement correction. However, personalized injury profiles revealed a greater number of clusters with reduced FA in SWM compared to DWM in youth with a history of TBI.
Conclusions: These results suggest that SWM may be more sensitive than DWM to axonal injury following TBI. Additionally, the heterogeneous nature of TBI may limit the ability of DTI studies to identify regions of microstructural alterations in group wise analyses, thus personalized injury profiles may be a more sensitive biomarker of injury.
Supported By: Hospital for Sick Children - Restracomp
Keywords: Traumatic Brain Injury, White Matter Microstructure, Short-Distance Tracts, Developing Brain

F67. Increased Amygdalar Activation to Angry Faces is Linked to Reduced Prefrontal Cortical Thickness and Hyperactive/Inattentive Symptomatology in Adolescents

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Background: Prior studies have reported increased amygdalar activation in response to emotional stimuli among individuals with attention-deficit/hyperactivity disorder (ADHD). Herein, we investigate the extent to which amygdalar activation to angry faces is associated with ADHD symptomology and cortical morphology in a population-based sample of adolescents.
Methods: Data were obtained from the IMAGEN study, which includes 2,223 adolescents. While undergoing functional imaging, participants passively viewed video clips of a face that started from a neutral expression and progressively turned angry, or, instead, turned to a second neutral expression. Left and right amygdala ROIs were used to extract mean BOLD signal from the angry face minus neutral face contrast for all subjects. T1-weighted images were processed through the CIVET pipeline (version 2.1.0). ADHD

symptomatology was assessed using the Development and Well-Being Assessment, and Strengths and Difficulties Questionnaire.
Results: Youths exhibiting increased left amygdalar activation (+1.5 SDs) (92 participants; 40 females) possessed significantly greater parent- and self-reported ADHD symptomatology relative to all other subjects ($p = .012$-$.038$). Compared to the rest of the sample, youths exhibiting increased left amygdalar activation did not differ with regard to demographic variables, or other forms of psychopathology, including mood/anxiety symptoms. Increased amygdalar activation was associated with reduced cortical thickness in orbital/ventromedial prefrontal regions. Further analysis revealed significant negative associations between parent-reported ADHD symptoms and thickness in orbital/ventromedial prefrontal cortices—cortical thickness in these regions was negatively correlated with left amygdalar activation.
Conclusions: These findings suggest that cortico-amygdalar circuitry may underpin aspects of core ADHD symptomatology, not simply co-occurring mood and anxiety problems.
Keywords: ADHD, Amygdala, Faces, Surface-Based Morphometry, Inattention

F68. Neural Correlates of Reward Expectation in Pediatric OCD

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Background: Neuroimaging findings from adults with Obsessive-compulsive disorder (OCD) suggest dysfunction in reward-based learning processes. However, less is known about these processes and the underlying circuits in youth with OCD.
Methods: Functional magnetic resonance images (fMRI) were acquired from 25 children/adolescents with OCD (age: M=12.5, SD=3) and 23 age- and gender-matched healthy controls (HC) (age: M=11, SD=3) while performing a virtual reality-based task analogous to the "win-shift" version of a radial maze task used in rodents. The task included a condition in which spatial cues were helpful in locating rewards and reward expectation was high (A) and a control condition in which reward locations were randomized and thus rewards were unexpected (B). Task events were classified as searching, anticipation, reward receipt, and no reward.
Results: An omnibus analysis revealed group x condition x event interactions in cingulo-opercular regions, including inferior frontal gyrus (IFG) and dorsal anterior cingulate cortex (dACC; $p<0.001$, FDRc $p<.05$). Whereas OCD participants activated these regions in response to receiving unexpected rewards in condition B (positive prediction errors [PE]), HC participants activated dACC in response to receiving expected rewards in condition A. Whereas the OCD group showed IFG deactivation when not receiving expected rewards in condition A (negative PE), the HC group deactivated this region when not receiving (unexpected) rewards in condition B.
Conclusions: Our findings suggest altered functioning of the cingulo-opercular circuit associated with reward expectation in youth with OCD. PE signaling might elicit their recruitment of this circuit in the service of inhibiting anxiety associated with false expectations.
Supported By: R21MH101441
Keywords: Pediatric OCD, Functional MRI, Cingulo-Opercular Circuit, Reward

F69. Salience Network Connectivity in Children With Nonverbal Learning Disability or Autism Spectrum Disorder

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Background: NonVerbal Learning Disability (NVLD) is characterized by deficits in spatial reasoning, executive functioning, fine-motor skills, math, and social functioning. Due to a number of clinical similarities, there is debate as to whether NVLD should be classified as a sub-type of Autism Spectrum Disorder (ASD) or as a discrete diagnosis. Herein, we use resting state fMRI (rsfMRI) to assess whether the social deficits seen in NVLD and ASD arise from different patterns of brain connectivity.
Methods: rsfMRI data was acquired from 20 typically developing and 21 children with NVLD, as well as 20 typically developing and 17 children with ASD from the Autism Brain Imaging Data Exchange-II (all matched on age and sex). Bivariate correlations between 7 seeds of the salience and 4 of the default mode networks were examined. Second-level F-tests were performed in CONN to examine differences in ROI-to-ROI connectivity as a function of diagnostic group. Univariate GLMs parsed group effects.
Results: Five ROI-to-ROI connections in the salience network showed significant group differences. Children with NVLD showed decreased anterior cingulate-anterior insula connectivity, whereas children with ASD showed increased supramarginal gyrus-rostral prefrontal cortex connectivity. Connectivity between these regions was associated with scores on the Social Responsiveness Scale. No group differences within or between the default mode network were detected.
Conclusions: This is the first study of rsfMRI in children with NVLD. Findings suggest that the social deficits in NVLD and ASD arise from different patterns of altered connectivity within the salience network, and that NVLD is distinct from ASD.
Supported By: The NVLD Project, NIEHS K23ES026239
Keywords: Neuroimaging, Resting State Functional MRI, Autism Spectrum Disorder, NonVerbal Learning Disability, Social Processing

F70. Functional Connectivity of Thalamocortical Circuitry in Autism Spectrum Disorder (ASD)

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Background: Genetic studies point to the thalamic reticular nucleus (TRN) in the pathogenesis of ASD. The TRN modulates sensory processing and attention by gating thalamocortical communication during wake, and propagates spindles during sleep (oscillations critical for memory consolidation). Here, we investigated whether thalamocortical functional connectivity is abnormal in ASD. Because motion artifacts may create spurious group differences, we used pre-scan training and strict data quality inclusion criteria to prevent and control for motion confounds.
Methods: 51 ASD and 36 typically-developing (TD) individuals, aged 8-25 participated in a resting-state fMRI study. The final sample after exclusion for motion was 34 ASD and 35 TD (matched for demographic and data quality measures). We performed seed-to-voxel connectivity analysis using thalamic seeds from the FSL-Oxford-Thalamic-Connectivity atlas. Following standard preprocessing, motion artifacts and physiological noise were regressed out and thalamocortical connectivity was computed. Regression analysis was used to examine group differences and relations with age (we report pFDR$\leq$.05).
Results: Relative to TD, ASD exhibited increased connectivity of thalamus with bilateral temporal auditory cortex (BA 21), and reduced connectivity with left anterior cerebellum. Age correlated negatively with thalamocortical connectivity in both groups in left visual association cortex (BA18) and right temporal pole (BA 38) There were no group differences in the relations of age with thalamocortical functional connectivity.
Conclusions: Increased connectivity of the thalamus with bilateral auditory association areas in ASD may reflect reduced inhibitory control of the TRN on thalamocortical communication. This may contribute to abnormal sensory processing and integration.
Supported By: U.S. Department of Defense Idea Award AR100312P1 to DSM & SLS; National Heart, Lung, and Blood Institute 5T32HL007901-1 to BB
Keywords: Autism Spectrum Disorder, Resting State Functional Connectivity, Thalamocortical Circuitry

F71. Cortical Abnormalities Associated With Anorexia Nervosa

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Background: Anorexia nervosa (AN) is an eating disorder with a moderate - high heritability. Cortical folding refers to the pattern of ridges and furrows observable on the cortex and is thought to remain relatively invariant after birth. Therefore, differences seen in psychiatric disorders have been proposed as early biomarkers, or used as intermediate phenotypes in imaging genetics studies.
Methods: We collected high resolution structural MR images in acutely underweight adolescent female AN patients (n=63), long-term recovered patients (n=41) and healthy controls (n=93). The majority of acutely ill patients were scanned again after partial weight normalization (> 10% BMI increase). Images were subjected to an automated longitudinal processing software and both the local gyrification index (LoG) and absolute mean curvature (aMeC) were computed vertex-wise.
Results: While gyrification was broadly reduced in acutely ill patients, normal values were restored in most brain regions after brief weight gain, and after full recovery no significant differences were evident relative to controls. Increased gyrification was largely predicted by weight restoration alone, while the effect of comorbid depression and hydration status was negligible. At the same time, we found aMeC to be increased in the acute state, but to normalize after weight gain.
Conclusions: These findings reveal that reduced LoG and increased AMC can occur at the same time and describe different aspects of cortical folding. Moreover, they support that macroscopic changes in cortical folding in AN are more reflective of nutritional state than premorbid trait- or biomarkers, and that they can be reversed rapidly if therapy is started promptly.
Supported By: DFG
Keywords: Anorexia Nervosa, MR Structural Imaging, Weight Gain

F72. Effect of Weight Restoration on Neural Networks Associated With Rumination in Anorexia Nervosa

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Background: Rumination, a form of cognitive rigidity, may contribute to the chronic course of Anorexia Nervosa (AN). Resting state functional-connectivity MRI was used to examine the hypothesis that neural networks associated with rumination symptoms would differ between AN and healthy controls (HC), both before and after treatment.
Methods: Hospitalized females with AN (n=26) were compared with age-matched HC (n=28) before and after weight restoration for AN, and approximately two months apart for HC. Independent components analysis was used to examine the Executive Control Network (ECN), Default Mode Network (DMN), and Salience Network (SN). Rumination was measured with the Ruminative Responses Scale (RRS).
Results: Network coupling between the SN and ECN was reduced in AN relative to HC before and after weight restoration (T1: t=3.13, p=0.004; T2: t=3.06, p=0.005). Among AN, there was significantly reduced connectivity within the SN between the thalamus and posterior insula which persisted after weight restoration (T1: t= -1.94, p=0.029, T2: t=-1.71, p=0.047) and was significantly or trend-level associated with components of rumination: reflection (T1: r=0.489, p=0.011; T2: r=0.376, p=0.058) and brooding (T1: r=0.362, p=0.069; T2: r=0.407, p=0.039).

Conclusions: We identified functional connectivity alterations in RSNs involved in cognitive control and emotional processing in AN which persisted following weight restoration and were associated with behavioral measures of rumination. These findings suggest abnormalities in these neural networks may contribute to the persistence of ruminative preoccupations about eating, weight and shape in weight-restored AN.
Supported By: NIMH
Keywords: Anorexia Nervosa, Resting State Functional Connectivity, Rumination

F73. Neural Markers of Longer Term Outcome in Anorexia Nervosa

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Background: Obesssionality has long been observed in anorexia nervosa (AN), and has been associated with mesolimbic system disturbances in other psychiatric illnesses. We have shown mesolimbic hyperconnectivity in AN. To better understand this phenomenon, we examined mesolimbic connectivity along with psychological symptoms (obessionality and rumination) and how these relate to post-hospital course.
Methods: Hospitalized females with AN (n=26) participated in a resting state fMRI scan upon admission and after weight restoration, and were compared with healthy volunteers (n=24). Participants completed the Obsessive Compulsive Inventory, revised (OCI-R) and the Ruminative Response Scale (RRS). Imaging analyses included resting state functional connectivity of the mesolimbic system, and network coupling between three related to cognitive rigidity. Among AN, weight was assessed for 4 weeks after hospital discharge to determine rate of weight loss after treatment (a proxy for longer-term outcome).
Results: Psychological symptoms showed minimal to no change with weight restoration (OCI-R: $F1,48=3.8$, $p=0.06$; RRS: $F1,45=1.95$, $p=0.17$), and were associated with weight loss (OCI-R: $r=-0.51$, $p=0.01$; RRS: $r=-0.43$, $p=0.04$). Consistent with prior findings, AN showed increased nucleus accumbens-orbitofrontal cortex connectivity at admission ($pcorr<0.05$; $puncorr=0.002$, $k=29$). Network coupling between the Salience and Executive Control networks was reduced in AN before and after weight restoration ($p=0.0006$ and $p=0.003$, respectively).
Conclusions: Measures of cognitive rigidity are slow to change in AN, and relate to prognosis. Some, but not all, connectivity findings suggest abnormalities in related neural systems. The quest for identifying biomarkers lies in the pursuit of the links between these three levels - symptoms, brain systems, and weight loss.
Supported By: R21
Keywords: Anorexia Nervosa, Obsessionality, Resting State fMRI, Outcome

F74. Frequency of Nonsuicidal Self-Injury Associated With Amygdala Functional Connectivity

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Background: Little is known about neurobiology associated with severity of nonsuicidal self-injury (NSSI). One index of NSSI severity is the frequency in which one engages in an episode of NSSI. Extending on prior work implicating disruptions in amygdala resting-state functional connectivity (RSFC) in patients with NSSI compared to controls, the present study examined the association between amygdala RSFC and frequency of NSSI episodes.
Methods: Twenty-five females aged 13-21 with NSSI completed a six-minute resting-state fMRI scan. Frequency of NSSI episodes per week was calculated using consensus between clinician-administered and self-report measures. Frequency was entered as a main regressor for separate right and left amygdala whole-brain RSFC comparisons. Age was entered as a covariate of no interest. We used a cluster z-threshold of 3.09 and corrected $p<.05$.
Results: Greater weekly NSSI episodes was associated with higher amygdala RSFC with bilateral frontal pole, middle frontal gyrus, lateral occipital cortex, cerebellum, and precuneus, and right hippocampus and posterior cingulate cortex. Conversely, greater weekly NSSI episodes was associated with lower amygdala RSFC with bilateral caudate, left middle temporal gyrus, insula, and precentral gyrus.
Conclusions: Findings suggest that those who engage in NSSI more frequently have higher levels of amygdala involvement with regions implicated in self-referential processing, memory, and attention. Additionally, greater NSSI frequency was also associated with lower levels of amygdala involvement with regions implicated in reward processing, decision making, and interoceptive awareness. Additional research is needed to explore whether there are other clinical measures associated with these connectivity patterns, which may further inform future neurobiologically targeted interventions.
Supported By: NIMH R21; University of Minnesota Academic Health Center Faculty Research Development Grant Program
Keywords: Non-suicidal Self-Injury, Resting State Functional Connectivity, Amygdala, Adolescence

F75. Selective Attention Processes in ADHD: Evidence From a Modified Stroop- Flanker Task

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Background: Individuals with Attention Deficit/Hyperactive Disorder (ADHD) were shown to have inhibition and inattention

deficits that might be associated with high distractibility. Thus far, studies explored ADHD distractibility have mainly applied conflict tasks, and did not consider the distractors' relevance to the task. Our study aims to focus on relevance-based distractibility and on possible differences between ADHD adults compared with controls in interference, and their modulation by task-relevance.
Methods: 37 adults (18 ADHD, 19 controls) participated in a Flanker localization task during event related potentials (ERPs) recording. Participants responded to the location of a central arrow while ignoring two distracting peripheral arrows. The flankers had task-relevant (i.e. location) and task-irrelevant (i.e. direction) dimensions (Lichtestein-Vidne et al., 2007;2012).
Results: Task-relevant dimension: For the controls behavioral congruency effect was observed. This effect was further shown for both N2 and N450 ERP components. For the ADHD group, conflict resolution was found only in the neural findings (N2 and N450 amplitudes), while such effect was not present behaviorally. Task-irrelevant dimension: Neural findings revealed dissociation between ADHD and controls; while congruency effect for task-irrelevant information was shown for the controls in the P2 component, this effect was not documented in the ADHD group.
Conclusions: Our findings demonstrate abnormalities in conflict resolution among adults with ADHD. The results suggest differences in basic visual processing and might explained in terms of adaptation; Controls processed the visual information fully and reacted to the relevant one, whereas ADHD individuals processed only the relevant information, and did not react to neither of the dimensions.
Keywords: Attentional Control, Attention Deficit Hyperactivity Disorder, Event Related Potentials

F76. Cortical Thickness and Voxel-Based Morphometry in Combat Veterans Suffering From Impulsive Aggression

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Background: Problems with impulsive aggression occur in many forms of psychiatric dysfunction, and are a common complaint among combat veterans. The present study sought to examine the potential neuroanatomical markers of combat-related impulsive aggression.
Methods: T1-weighted magnetic resonance images (MRI) were acquired from 28 male veterans with, and 30 veterans without impulsive aggression problems. Voxel-based morphometry and cortical thickness analyses were conducted, focusing on the following regions-of-interest: the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), basolateral amygdala (BLA), and centromedial amygdala (CMA).
Results: Statistical analyses yielded no significant group differences for any of the a priori regions-of-interest (all $p > 0.05$, corrected for the number of comparisons). Instead, exploratory spatial analyses indicated a significant reduction in cortical thickness of a locus in the left cuneus in the impulsive aggression group, relative to the non-aggressive combat controls (cluster-wise p-value = 0.02, maximum observed at x = -8.9, y = -75.9, z = 12.7).
Conclusions: This finding is in line with recently published resting-state fMRI data by our group, in which a significant group difference in functional connectivity was recorded between the (bilateral) ACC and a cluster centered around the left cuneus—the location of which strongly corresponds to the cuneus locus reported here. Taken together, these findings point to a role for the cuneus as an important neural mediator of impulsive aggression problems in combat veterans.
Supported By: Dutch Ministry of Defense
Keywords: Impulsive-Aggresive, Voxel Based Morphometry, Cortical Thickness, War Veterans

F77. Effect of Transcranial Infrared Laser Stimulation to Left Prefrontal Cortex on Verbal Cognition

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Background: Transcranial Infrared Laser Stimulation (TILS) is a non-invasive form of neuromodulation with therapeutic potential that enhances performance in tasks of attention, executive function, and short-term memory through a mechanism involving increased cortical metabolic energy. In this study we sought to investigate the effect of TILS on verbal cognition using the Stroop task, which is associated with increased left prefrontal cortex (PFC) activity.
Methods: 40 healthy undergraduate volunteers (mean age 19.0 years, 27 females) performed the color Stroop task before and immediately after a single treatment with either sham (n=20) or TILS (n=20) to left PFC (8 min, 250 mW/cm2, 1064 nm). The number of errors and reaction times for correct trials of congruent and incongruent stimuli were analyzed using 2-way repeated measure ANOVAs.
Results: The Stroop effect of increased reaction times for color-word incongruent trials relative to congruent trials was observed as expected ($p<0.001$). No statistically significant interaction was observed between TILS treatment to left PFC and reaction times for congruent vs. incongruent trials when responding was based on either semantic meaning or printed color of the stimulus. No effect of TILS was observed on error rates.
Conclusions: The present results suggest that the cognitive enhancing properties of TILS do not extend to performance in an interference task of verbal cognition when applied as a single treatment to the left PFC in healthy young adults. Possible explanations include the role of subcortical structures or practical limitations of a single treatment, which have implications for therapeutic application of TILS.
Keywords: Neurostimulation, Low Level Laser Therapy, Prefrontal Cortex, Stroop

F78. The Effect of Fecal Microbiota Transplantation on Psychiatric Symptoms Among Patients With Functional Gastrointestinal Disorders: An Open-Label Observational Study

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Background: The intestinal microbiota is considered as a potential common underpinning pathophysiology of functional gastrointestinal disorders (FGIDs) and psychiatric disorders such as depression and anxiety, explaining the high comorbidity of both disorders. Fecal Microbiota Transplantation (FMT) has been reported to have therapeutic effects on diseases related to dysbiosis, but few studies have evaluated its effect on psychiatric symptoms.
Methods: We followed 17 patients with FGIDs who underwent FMT to treat their bowel symptoms and observed their psychiatric symptoms during the FMT. The changes of Hamilton Rating Scale for Depression (HAM-D) total score, and its subscale of sleep-related items, Hamilton Rating Scale for Anxiety (HAM-A), and Quick Inventory for Depressive Symptoms (QIDS) from baseline to 4 weeks were examined. We used 16SrRNA sequencing method to determine the microbiota composition of each sample, and Shannon index was used to express its diversity.
Results: Significant improvement in HAM-D total and sleep subscale score, HAM-A, and QIDS were observed ($p=0.008$, $p=0.008$, $p=0.01$, $p=0.006$, respectively). A subgroup of 8 patients whose gastrointestinal symptoms did not respond to FMT, also showed trend-level improvement in their HAM-D total and sleep subscale scores ($p= 0.066$, $p=0.066$, respectively). There was a significant correlation between baseline Shannon index and HAM-D score ($R=-0.57$, $p=0.03$), as well as Shannon index change and HAM-D improvement ($R=0.58$, $p=0.03$).
Conclusions: Depression and anxiety symptoms among patients with FGIDs were improved after FMT. Moreover, microbiota diversity was negatively correlated with depression severity. A larger study with a control group is needed in the future.
Keywords: Gut Microbiome, Depression, Anxiety, Fecal Microbiota Transplant, Dysbiosis

F79. Emotionally Dictated Hallucinations in Temporal Lobe Epilepsy

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[1]NA

Background: Temporal lobe epilepsy (TLE) with emotions preceding and congruent with the content of sensory hallucinations, has not heretofore been described.
Methods: Case Study: A 27 year-old male presented with a history of sensory hallucinations since the age of five. These hallucinations can last from seconds to hours, occurring up to 100 times a day. The visual hallucinations can be of living things or objects, which appear as a single entity or in groups of up to 50. They are either familiar or strangers, appearing alive, dead, or decapitated, and differ in age, complexion, gender, and size. Emotions impact the content of the visual hallucinations. When in fear, the hallucinations will either start decomposing or harm itself. During a sad state, the hallucinations will stare at him, but when angry, they begin to act negatively with nastiness, vileness, and in an unempathic nature. He admits to frequent déjà-vu, and denies drug use. Phenytoin was prescribed, and once therapeutic level was achieved, his hallucinations and unprovoked emotional responses, whether independent or concurrent, resolved.
Results: Abnormalities in neurological examinations: Cranial Nerve (CN): CN III, IV, VI: bilateral ptosis. Motor: Drift Testing: right upward-outward drift, cerebellar spooning, and abductor digiti minimi sign positive. Reflexes: 1+ throughout. Hoffman Reflex: positive bilaterally. Neuropsychological Testing: Go-No-Go and Animal Fluency Testing: normal. Magnetic resonance imaging of brain with/without infusion: normal. Five-day electroencephalogram: Temporal lobe status epilepticus with bilateral foci.
Conclusions: Those suffering from sporadic episodes of intense hallucinations and strong emotional states without clear evidence of psychosis warrant evaluation for TLE.
Supported By: Smell and Taste Treatment and Research Foundation
Keywords: Temporal lobe Epilepsy, Schizophrenia, Auditory Hallucination, Emotion, Seizures

F80. Sex Differences in Incidence and Predictors of Depression and Posttraumatic Stress Symptoms Among African Americans Experiencing Motor Vehicle Collision

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Background: Evidence suggests that African Americans (AAs) experience increased rates of adverse posttraumatic neuropsychiatric sequelae (APNS) versus non-Hispanic whites, but few prospective studies of APNS development have been performed in this understudied population. In this analysis, we evaluated for sex differences in the rates of posttraumatic

depressive symptoms (PDS) and posttraumatic stress symptoms (PTSS) in AAs experiencing MVC.
Methods: AA individuals presenting to the Emergency Department (ED) within 24 hours of MVC were enrolled. Six-week follow-up surveys included an evaluation of PDS (CES-D) and PTSS (IES-R). Multivariate regression analyses adjusting for study site and participant age were used to assess the influence of sex on PDS and PTSS. In secondary analyses, ensemble learning (Random Forest) methods were used to identify the most influential predictors of these outcomes in women and men.
Results: Participants (n=927, 62% female) presenting to the ED for care following MVC were enrolled. Six-week follow-up survey data was obtained in 85%. AA women had higher PDS scores ($F=4.733$, $p=0.030$) and higher PTSS scores ($F=4.216$, $p=0.040$) six weeks after MVC than men. Secondary analyses identified substantial sex differences in predictive factors. For example, among AA women the most strongly associated individual factors included both peritraumatic psychological factors (e.g., dissociation, loss of control) and pain severity, whereas in men such factors included only psychological characteristics (e.g. distress, catastrophizing).
Conclusions: Among AAs experiencing MVC, DPS and PTSS are more prevalent in women than men. Epidemiologic risk factors also differ in women and men, suggesting potential differences in underlying pathogenic mechanisms.
Supported By: Funding for this study was provided by NIAMS R01AR060852
Keywords: Posttraumatic Stress Disorder, Sex differences, Depressive Symptoms, Motor Vehicle Collision, African American

F81. Atypical Functional Connectome Hierarchy in Autism

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Background: Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition, with impairments in sensory processing and social cognition. Such deficits both in low- and high-level functions suggest an association to atypical functional hierarchy. Here we assessed this hypothesis using connectome-wide diffusion embedding, a non-linear technique to synoptically map a functional connectivity gradient from sensory to default mode regions.
Methods: The discovery dataset was based on resting-state fMRI data in 103 males with ASD and 108 typical males. Using diffusion embedding, we mapped the principal gradient of spatial variations in whole-brain connectivity. Surface-based models compared gradient magnitude between ASD and controls, controlling for site/age effects. Findings were complemented by systematic analyses of rich-club organization and long/short range connectivity profiling. To assess robustness, we repeated the analyses in an independent dataset (60 ASD, 59 controls).
Results: Compared to controls, ASD revealed decreased gradients in core DMN hubs, including medial prefrontal and parietal regions. Conversely, we observed increased gradients in unimodal association areas. DMN gradient reductions were associated with perturbed rich club connectivity across both short- and long-ranges, while unimodal cortices show connectivity alterations at mid-range, primarily to sensory-motor regions. Gradient findings were replicated in the separate dataset.
Conclusions: As hypothesized, both low- and high-level components along the functional hierarchy were affected in ASD, showing diverging patterns in connectome- and physical-space anomalies. Although the behavioral relevance of these network reconfigurations remains to be determined, they may differentially relate to anomalies in sensory integration and social cognition, commonly seen at the phenotypic level.
Supported By: Canadian League Against Epilepsy, CIHR Foundation/SickKids
Keywords: Autism Spectrum Disorder, Cortical Hierarchy, Resting State Functional Connectivity, Connectome Gradient

F82. Latent Factors of Psychopathology and Functional Connectivity of the Dorsal Anterior Cingulate Cortex During Reward Anticipation

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Background: Psychiatric disorders can be organized into the higher order latent factors of internalizing and externalizing as well as a general bifactor to account for overlap across disorders. The dorsal anterior cingulate cortex (dACC) has been identified as a possible neural substrate of this general bifactor. The current study examined the relationship between latent factors of psychopathology and functional connectivity (FC) of the dACC during reward anticipation.
Methods: 339 subjects (172 women, 26.09 ± 1.81 y.o.) from the Tennessee Twin Study (TTS) completed a structured clinical interview and the Monetary Incentive Delay Task. Beta series were extracted from the left dACC and the bilateral caudate during the anticipation phase of reward trials ($1 and $5). Correlations were run between pairs of regions for each reward type and then averaged to produce a single measure of FC. Multiple regressions were run with FC as the independent variable and latent factors as dependent variables. These regressions took stratification and clustering within twin pairs into account and covaried for relevant demographic variables.
Results: FC was not a significant predictor of the externalizing or general factors ($ps > .10$). FC was a significant predictor of internalizing ($\beta = .88$, $p < .05$).

Conclusions: Findings suggest that increased dACC FC during reward anticipation may be linked more specifically to internalizing psychopathology rather than shared across all disorders.
Supported By: 3R01MH098098-03S1; T32-MH18921
Keywords: Reward, Functional Brain Connectivity, Internalizing Symptoms

F83. Activity in Multiple Stress Systems Distinguishes Depressed Patients' and Suicide Attempters' Response to Social Stress

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Background: Dysregulation of the stress response may involve both the HPA axis as well as the sympathetic adrenomedullary system (SAM). The Trier Social Stress Test (TSST) paradigm produces transient increases in stress and accompanying changes to both cortisol and alpha-amylase (a proxy for noradrenergic activity) that can be measured via saliva.
Methods: A modified TSST was administered to 107 unmedicated patients with current major depressive episode (26 with prior suicide attempt, 81 without) and 76 healthy volunteers. Salivary cortisol, alpha-amylase and heart rate were assessed pre-stress and at five timepoints afterwards. Heart rate, mood and subjective ratings were also collected.
Results: The TSST produced expected increases in all groups in subjective distress, heart rate, cortisol and alpha-amylase. All depressed patients exhibited a reduced ratio of total output of alpha-amylase to cortisol (ratio of AUCs with respect to ground: $F[2,147]=3.31$, $p=.039$). Suicide attempters, in turn, exhibited a higher and later peak cortisol (time by group effect: $F[8,696]=1.95$, $p=.05$), as well as reduced alpha-amylase output at non-stress time points (time by group effect: $F[4,572]=2.57$, $p=.037$).
Conclusions: Social stress was associated with relatively reduced alpha-amylase and elevated cortisol output in all depressed patients. Suicide attempters, in turn, exhibited an altered time course of response, with later peak cortisol and a return to lower levels of alpha-amylase output after stress. Data suggest a combination of dysfunctions in the HPA and SAM stress systems is associated with both depression and risk for suicidal behavior.
Supported By: NIMH
Keywords: Suicide, Trier Social Stress Test, Depression

F84. Towards a Neural Profile of Disruptive Mood Dysregulation Disorder: An EEG Study of Emotional Face Processing

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Background: DMDD is a childhood disorder characterized by emotional and behavioral dysregulation involving negative mood and temper outbursts. The pathophysiological correlates of this symptom presentation remain poorly understood. Using emotional faces, we aimed to identify a neurophysiological profile associated with internalizing and externalizing symptoms characteristic of DMDD.
Methods: Thirty-four children (age: M=10.05) were diagnosed through KSADS. Parents completed the Child Behavior Checklist for symptoms. Youths participated in an EEG while completing an implicit emotional face task. Data were captured from central and right-hemisphere electrodes: Pz (central-parietal; 300-400ms), P8 (occipito-temporal: 250-350ms) and O2 (occipital: 200-300ms).
Results: In response to fear faces, the P300 latency to peak was associated with more withdrawal ($R2= .17$, $p=.03$), rule-breaking ($R2= .18$, $p=.03$), and aggression ($R2= .18$, $p=.03$). Withdrawal, rule-breaking ($R2= .28$, $p=<.01$), and conduct ($R2= .20$, $p=.02$) were also related to greater P8 response. However, O8 activity predicted less withdrawal and affective problems ($R2 =.20$ and .21 respectively; $ps<.04$).

In response to calm faces, greater latency to peak predicted withdrawal. P8 activity to calm faces predicted depression ($R2= .15$, $p=.05$), withdrawal ($R2= .28$, $p=.<.01$), rule-breaking ($R2= .38$, $p=<.01$) and conduct problems ($R2= .32$, $p=<.01$). Finally, greater peak amplitude at the O2 electrode predicted less depression and withdrawal ($R2 =.22$ and .21 respectively; $ps<.02$).
Conclusions: Greater responsivity to calm and fear in occipital regions predicted fewer internalizing symptoms. Greater externalizing symptoms were found in those with more responsivity and less efficient processing of fear in occipital-temporal and midline areas. Neural response to emotional faces may predict symptom presentations in DMDD.
Supported By: (RO1) MH 93582
Keywords: Mood Disorders, EEG, Neurophysiology

F85. An Electrophysiological Biomarker That Predicts Treatment Response to ECT

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Background: Electroconvulsive therapy (ECT) is the most effective treatment for major depression (MDD), but also carries risk of cognitive side-effects. The ability to predict whether treatment will be effective prior to initiation of treatment could significantly improve quality of care, reduce suffering, and diminish costs. In this study, we sought to carry out a comprehensive and definitive study of the relationship between the background electroencephalography (EEG) and therapeutic response to ECT.
Methods: Twenty-one channel resting EEG was collected pre-ECT and 2-3 days following ECT course from two separate data sets, one to develop an EEG model of therapeutic response (N=30) and a second to test this model (N=40). A 3-way principal components analysis was applied and

coherence and spectral amplitude across 6 frequency bands were examined. Clinical outcome measures included the Montgomery Asberg Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS).
Results: Four patterns of amplitude and coherence along with baseline MADRS score accounted for 85% of the variance in post-treatment course MADRS score in Study 1 ($R2=0.85$, $F=11.7$, $p<0.0002$) and 53% of the variance in HDRS score in Study 2 ($R2=0.53$, $F=5.5$, $p<0.003$). Greater pre-ECT course anterior delta coherence accounted for the majority of variance in therapeutic response (Study1: $R2=0.44$, $p = 0.01$; Study2: $R2=0.16$,$p = 0.008$).
Conclusions: These results suggest a putative electrophysiological biomarker that can predict therapeutic response prior to a course of ECT. Greater baseline anterior delta coherence is significantly associated with a better subsequent therapeutic response and could be indicative of intact circuitry allowing for improved seizure propagation.
Keywords: Major Depression, Electroconvulsive Therapy (ECT), Predictive Biomarkers, Neural Oscillations

F86. Durability of Response to Subcallosal Cingulate Deep Brain Stimulation for Treatment Resistant Depression

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Background: Deep brain stimulation of the subcallosal cingulate white matter (SCC DBS) has been investigated as a treatment for refractory depression since 2005. Results have generally been favorable in small-scale, open-label trials, but the 6-month outcomes of a randomized, sham-controlled trial appeared disappointing. However, given illness chronicity, the duration of typical efficacy trials may be inadequate to capture the impact of this intervention.
Methods: Twenty-eight subjects with unipolar ($n=21$) or bipolar 2 depression ($n=7$) underwent SCC DBS surgery 01/2007−06/2013 (FDA IDE#G060028, Clinical trials.gov#NCT00367003). After one year of stimulation, subjects continued to be assessed twice yearly. Data here are through September 2016. The primary outcome measure is the Hamilton Depression Rating Scale-17 measured yearly, with treatment response defined as at least 50% improvement.
Results: 155 patient-years of data were analyzed. Mean duration of participation is 5.9 ± 2.2 years.Three subjects exited the study. Subjects met response criteria at 106 of 155 yearly depression assessments. Response rates at 1, 2, and 3 years are 53.6%, 74.1%, and 57.7%. At the time of last follow up, ($n=25$; range 3-9 years) 68% are responders, 44% are in remission, and the mean HDRS-17 score is 8.8 ± 5.6. Across 9 years, response rates have been maintained in $\geq$50% of patients and remission in $\geq$30%. 36% of subjects have maintained continuous response since first achieving responder status.
Conclusions: This naturalistic 9 year -study of SCC DBS in TRD demonstrates sustained response effects in the majority of patients with ongoing DBS.
Supported By: Dana Foundation; Hope for Depression Research Foundation; Stanley Medical Research Foundation; devices donated by St. Jude Medical Neuromodulation
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Longitudinal Study

F87. Rostral Anterior Cingulate Glutamate Levels are Linked to Abnormal High-Frequency Resting-State Functional Connectivity in Bipolar Disorder

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Background: Functional magnetic resonance imaging (fMRI) studies indicate that the emotional and cognitive symptoms of depression may be linked to aberrant resting-state functional connectivity (rsFC). However, much remains unknown about how abnormalities in higher frequency connectivity contribute to these disturbances. Furthermore, while concurrent evidence suggests glutamatergic abnormalities in the rostral anterior cingulate (rACC) may be implicated in depression and may contribute to disrupted rsFC, no study has examined whether these disturbances are linked in depressed populations.
Methods: High-frequency rsFC was measured using electroencephalography in 61 depressed individuals (17 with bipolar disorder) and 24 controls. The glutamate to glutamine ratio (Glu/Gln) in the rACC was measured using magnetic resonance spectroscopy. rsFC within the default mode network (DMN) and frontoparietal network (FPN) was computed in the delta, theta, alpha and beta frequencies.
Results: Group differences emerged for beta-band connectivity in the FPN, $F(2,82)=4.08$, $p=.02$. Specifically, the bipolar group had stronger connectivity compared to controls ($p=.02$), and marginally stronger connectivity relative to the unipolar group ($p=.095$). Although groups did not differ in rACC Glu/Gln ($p>.05$), within the bipolar group, stronger beta-band FPN connectivity correlated with rACC Glu/Gln ($r=.55$, $p=.03$) and manic symptomatology ($r=-.53$, $p=.04$).
Conclusions: These findings extend our understanding of the temporal dynamics of rsFC, showing that high-frequency rsFC in the FPN −a network critically implicated in emotion regulation − is associated with bipolar mood symptomatology. Furthermore, the findings build on prior work by showing that disruptions in rACC glutamate may drive aberrant high-frequency communication within this network, potentially leading to emotion dysregulation in bipolar disorder.
Supported By: NIMH RO1
Keywords: Bipolar Disorder, Depression, EEG, MRS, Neuroimaging

F88. A Transdiagnostic Study of Reward Processing Alterations in Adolescents Using the Monetary Incentive Delay Task

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Background: Studies repeatedly show that reward processing is altered across different psychiatric diagnoses. In depression, for example, individuals show altered neural responses during anticipation and feedback phases of reward processing, which is linked to anhedonia and aberrant modification of behavior towards rewards. In anxiety, reward processing is thought to be characterized by loss avoidance and increased sensitivity to losses.
Methods: Participants aged nine to eighteen diagnosed with major depressive disorder (MDD) (n=29), anxiety (n=13) and healthy volunteers (n=29), completed the MID task in an fMRI scanner. In each trial, the participant was exposed to one of three possible cue shapes which corresponded to obtaining or avoiding different monetary rewards. We compared the behavioral performance across diagnostic groups, including response times as well as target duration, which is predetermined by the tracking algorithm to maintain a fixed success rate.
Results: There were significant differences in performance across diagnostic groups. Overall, for participants diagnosed with anxiety preforming at the fixed success rate was hardest, while participants diagnosed with MDD preformed more similar to the healthy group. Participants diagnosed with MDD had significantly lower response times and target duration compared to those diagnosed with anxiety and healthy volunteers (MDD v. HV p=0.036, MDD v. Anxious p=0.002).
Conclusions: It is possible that these behavioral differences in performance are indicative of differences in the sensitivity to wins and losses. These differences may need to be take into account when analyzing brain correlates of reward processing transdiagnostically.
Supported By: NIMH Intramural Research Program
Keywords: Reward Processing, Major Depression, Anxiety, Monetary Incentive Delay Task, Transdiagnostic

F89. Reduced Fronto-Limbic Connectivity in Adolescents With Mood Disorders: Associations With Worse Depressive Symptomology and Cognitive Impairment

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Background: Mood disorders, including bipolar disorder and depression, often arise in adolescence, a time of ongoing neurodevelopment. Reduced recruitment of the prefrontal cortex and overactive amygdala may contribute to cognitive and emotion regulation impairments. These mechanisms are not fully understood in adolescence. This study used behavioral and neural measures to investigate the integrity of implicated neural circuits in mood disorders in adolescents.
Methods: Adolescents aged 13-18 years with a mood disorder (n=27) and healthy controls (n=15) completed the Attention Network Test (ANT) and a resting-state MRI. Whole-brain regression analyses were conducted with the amygdala seed and contrasts were run comparing patient and control groups with cluster $z > 2.3$ and $p < .05$.
Results: The mood disorders group showed significantly lower RSFC between right amygdala and a frontal region that included the anterior cingulate cortex (ACC). The mood disorders group had lower accuracy scores on the ANT compared to controls, t=2.29, p=.03. Across the entire sample, right amygdala-ACC connectivity negatively correlated with depression symptomology, r=-.48, p=.008 and showed a marginal positive correlation with accuracy on the ANT, r=.33, p=.08.
Conclusions: Patients showed reduced fronto-limbic circuitry compared to controls which was associated with greater depressive symptomology and worse attentional performance. This supports the role of fronto-limbic circuitry in mood disorders, and disrupted fronto-limbic connectivity may contribute to affective and cognitive symptoms in bipolar disorder and depression.
Supported By: Ontario Mental Health Foundation, Engdahl Family Research Fund
Keywords: Fronto-limbic Connectivity, Resting State fMRI, Mood Disorders, Cognitive Impairment

F90. Longitudinal Structural Covariance Associated With Antidepressant Electroconvulsive Therapy Response

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Background: Major depressive disorder (MDD) is highly prevalent and symptomatically heterogeneous. The Hamilton Depression Rating Scale (HDRS) total score is commonly used to evaluate clinical improvement regardless of symptom heterogeneity. Here, we explore how HDRS symptom dimensions covary with structural imaging measures during electroconvulsive therapy (ECT).
Methods: 157 ECT patients (age=49.5+/-4.3 years; 96 females) from 4 sites in the Global ECT-MRI Research Collaboration experiencing a DSM-IV defined MDD episode were included. Prior to and following ECT, patients underwent structural MRI and the17-item HDRS assessed symptoms. Bayesian estimation identified HDRS items credibly reduced by ECT; oblimin rotations identified the factor structure of these items. MRIs were segmented using FreeSurfer. Within-subject structural covariance was described by graph-based node degree distributions (NDD) from the pairwise ratios of regional percent structural changes over ECT. NDD was obtained by thresholding matrices of each subject's regional ratios at k successive levels to produce k adjacency matrices

from which NDD was calculated. NDD reflects a specific regions degree of change relative to other regions. Random forest regression related HDRS factors to NDD.
Results: Five HDRS items, depressed mood, guilt, suicide, work, and psychic anxiety, improved with ECT and loaded onto a single factor (F1). Permutation tests showed that the overall regression model significantly predicted F1 (RMSE=0.67;$p<0.01$). NDD of right anterior and medial temporal lobe structures were most associated with F1.
Conclusions: ECT robustly reduces a subset of core MDD symptoms. The reduction of these symptoms is associated with relative degrees of volumetric change in right temporal structures.
Supported By: R01MH092301; K24MH102743
Keywords: Major Depression, Electroconvulsive Therapy (ECT), Structural Magnetic Resonance Imaging, Machine Learning, Structural Connectivity

F91. Transdiagnostic Depressive Symptoms and Affective Blunting in an Internalizing Sample

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Background: Mounting evidence suggests that psychophysiological reactivity to negative stimuli is blunted in depression. For example, the late positive potential (LPP) – an event-related potential that is larger for emotional compared to neutral stimuli – is reduced among depressed individuals. However, little work has examined associations between depressive symptomatology and the LPP in a transdiagnostic, mixed internalizing sample.
Methods: Participants (N = 26) with a range of internalizing disorders viewed negative and neutral scenes as EEG was recorded. Participants completed depression subscales of the Personality Assessment Inventory (PAI). We performed continuous and categorical analyses to assess associations between depression and the LPP. We also compared depressive symptom scores for participants in the upper, lower, or medium third of LPP amplitude.
Results: Greater cognitive, affective and physiological depressive symptoms related to smaller LPPs (PAI; $|rs|=.40$-$.46$, $ps<.05$) for negative compared to neutral pictures. When the LPP was used to classify participants, the low reactivity group had higher overall PAI depression scores than medium reactivity, $t(15)=2.62$, $p=.03$, and high reactivity, $t(16)=2.08$, $p=.06$, groups, $F(2,23)=4.73$, $p=.02$. There were no significant categorical effects (presence/absence of depression) on the LPP.
Conclusions: Even among disorders thought to be associated with hyperactivity to negative stimuli (e.g., specific phobia, social anxiety disorder), increased depressive symptomatology is associated with reduced electrocortical response. Moreover, the LPP may provide a means of identifying participants whose pattern of physiological responding is at odds with their subjective experience, and who may therefore warrant a unique or adjunctive course of treatment.
Supported By: National Institute of Mental Health, K23 MH105553
Keywords: Depression, EEG, Transdiagnostic, Emotion, Research Domain Criteria (RDoC)

F92. Identification of Biotype in Anxiety and Depression Using Amygdala Response to Threat and Objective and Subjective Measures of Sleep

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Background: Anxiety and depression are heterogeneous internalizing psychopathologies (IPs) characterized by exaggerated amygdala reactivity to threat and problematic sleep to varying degrees. Therefore, measures of brain response to threat and sleep could be leveraged to identify novel subtypes of IPs.
Methods: During fMRI, 94 non-medicated individuals with either primary generalized anxiety disorder (n=27), social phobia (n=39), panic disorder (n=4), or major depression (n=24) completed a validated emotion processing task. Cluster analysis with log-likelihood and Bayesian Information Criterion procedures was performed on 3 units of measure, which were standardized – bilateral amygdala response to threat (>happy) faces derived from an anatomy-based mask, self-reported sleep quality (Pittsburgh Sleep Quality Index), and an objective/actigraphy estimate of sleep duration. Symptom measures (HAMA, HAMD) and brain data for amygdala and other regions for identified clusters were submitted to an ANOVA (Bonferroni corrected).
Results: Three clusters were identified; ANOVA revealed 'Biotype' 1 (n=36) had less anxiety (HAMA) and depression (HAMD) symptoms, better self-reported sleep quality, objectively longer sleep duration, and less neurofunctional activity in amygdala, dorsal anterior cingulate cortex, and insula to threat compared to Biotype 2 (n=23) (highest $p<0.03$). Additionally, Biotype 1 had fewer symptoms and better subjective and objective sleep than Biotype 3 (n=35) (highest $p<0.005$) but did not differ in neural activity to threat in any region.
Conclusions: Cluster analysis based on amygdala reactivity and sleep measures identified novel subtypes of IPs that cut-across current diagnostic boundaries. These data may be useful for identifying phenotypes, which has implications for disease classification and treatment.
Supported By: NIMH K23MH093679; NARSAD; NIMH R01MH101497
Keywords: Functional Neuroimaging, Sleep, Major Depression, Anxiety Disorders, Biotypes

F93. Gender Differences in Brain Activation During Implicit Emotional Processing in Patients With Melancholic Depression

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Background: Increased susceptibility of women to MDD may relate to differences in neural processing of emotional faces between men and women. Studies of gender differences in depression that include all subtypes may be skewed due to neural differences of subtypes. It is therefore valuable to investigate gender differences in samples that are homogeneous regarding depressive subtype. Gender differences may also be linked to neural dysregulation that occurs in melancholic depression, which is characterized by blunted emotional reactivity and significant anhedonia. The aim of this study was to investigate gender differences in the melancholic subtype as it relates to brain activation during implicit perception of emotional faces.
Methods: Thirty participants who met the DSM-IV criteria for a current major depressive episode (15 female) and 21 healthy age matched controls (12 female) underwent fMRI using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system while viewing sad, happy, fearful or neutral faces and determining the gender (Penn Emotional Faces, Gur et al., 1992). FMRI data were preprocessed using the AFNI package (Cox, 1996).
Results: ROI analyses from areas with significant gender*-group effects revealed decreased BOLD signal in right insula, and increased activation in right cingulate, precuneus, and left posterior cingulate cortex in women compare to men ($p \leq 0.005$). A gender*melalncholic score effect was found in the right superior temporal gyrus. Additionally, the lateralization index showed gender differences.
Conclusions: Gender differences in brain activation during implicit emotional processing exist in patients with melancholic features and may contribute to understanding greater susceptibility of women to MDD.
Supported By: Grant from XYZ and K23MH067705 to EBN, and AAUW International Postdoctoral grant to AMK.
Keywords: Major Depressive Disorder (MDD), Gender Differences, Melancholic Depression, BOLD Functional MRI, Emotional Face Processing

F94. Blunted Sleep Stage Related Heart Rate Variability in Antidepressant-Free Depression is Associated With Comorbid Sleep Disturbances

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Background: Heart rate variability (HRV), an indicator of the autonomous nervous system (ANS) activity, is blunted in major depression. However, effect sizes of studies in wakefulness are weak and may be overlaid by antidepressant (AD) effects. Therefore, we examined HRV related to sleep stages and compared AD-free patients with depression to healthy controls. Further we examined, if sleep stage related HRV in depression was correlated to subjective or objective sleep disturbances.
Methods: Thirty-four out-patients with major depression without AD treatment (age: 28 ± 8y; 55.6% females). HRV was assessed in 5-min segments from ECG of polysomnography (PSG) in pure and artefact free REM, N2 and N3 sleep. HRV frequency domain measures were compared between patients and controls. Sleep quality was assessed with both, subjective Pittsburgh Sleep Quality Questionnaire (PSQI) and objective PSG.
Results: In patients, HRV was blunted in all sleep stages (ANOVA main effect group: $p=.002$) discriminating patients from healthy controls with moderate to large effect sizes ($d=.45-.84$). Moreover, as patients presented with poor subjective sleep ($p<.001$), but not significantly reduced objective total sleep time (TST), blunted HRV in REM sleep correlated with both, higher (i.e. poorer) PSQI scores and decreased TST ($r=-.28^*$, $r=.43^{**}$, resp.).
Conclusions: Sleep stage related HRV discriminates patients with MDD from healthy controls with larger effect sizes than HRV in wakefulness independent from AD-effects. As blunted HRV is correlated with comorbid sleep problems, more severe insomnia may be a clinically indicator for more severe hyperarousal and increased cardiovascular risk.
Supported By: Forschungsförderungsfond der Universitären Psychiatrischen Kliniken Basel, Switzerland
Keywords: Depression, Heart Rate Variability, Insomnia, Polysomnography

F95. Pattern Separation: A Potential Marker for Adolescent Depression

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Background: Pattern separation, the ability to discriminate between similar, but not identical, stimuli, is dependent on hippocampal adult neurogenesis. Performance on pattern separation tasks appears inversely correlated with depressive symptoms in non-clinical samples.

As such, we examined performance on pattern separation in adolescents with major depressive disorder (MDD) and collected electrophysiological data.
Methods: Unmedicated 12 to 17 year-old participants were enrolled and administered the MINI International Psychiatric Interview, a structured clinical interview, and several rating scales. They completed the Mnemonic Similarity Task (MST), where similar pictures must be recognized as "new" the first time they are displayed and as "similar", but not identical, the second time.

EEG data were collected using a 32-channel Brain Vision EEG system based on the international 10/20 system. Event-related potentials corresponding to performance on the MST were computed for each participant and averaged across groups.
Results: Twenty-four participants (20 ♀, age: 14.7±1.6 yrs, 16 with MDD, time since MDD onset: 2.6±1.8 yrs) were enrolled. Adolescents with MDD correctly identified 56% of the "Similar" stimuli compared to 67% of healthy controls ($p=0.0486$). The lure discrimination index, which corrects for response bias, was significantly inversely associated with depression severity ($r= -0.42$, $p=0.0385$). At Pz electrode placement, P300 activity during pattern separation differed between the two groups ($p=0.0336$).

Conclusions: Performance on pattern separation appears impaired in adolescents with MDD and this is associated with electrophysiological differences. Further research will seek to further characterize this deficit in order to examine its potential as a biomarker for adolescent depression.
Keywords: Adolescent Depression, Pattern Separation, Neurophysiology, Biomarkers

F96. Irritability Influences Relations Between Social Functioning Deficits and Neural Response to Unpredictable Social Evaluation

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Background: In adolescence peer-relations are increasingly important, and experiences of social rejection coupled with risk factors, such as social impairment and irritability, can lead to the onset of mental health problems. Unpredictable peer interactions are highly salient and may provoke anxiety because there is a potential for social rejection. Social impairment has been linked to irritability, an emotional state that is a key symptom across several mental health disorders. Isolating neural mechanisms of social processing and irritability may provide novel targets for early interventions for individuals with social impairment.
Methods: In an ongoing study, 11-14 year olds (N=31) completed the fMRI-based Virtual School paradigm. Brain function was modeled during real-time interactions with "Other Students" who have reputations for being 'nice', 'unpredictable', or 'bullies'. Parent report on the Social Skills Improvement System (SSIS) quantified social communication, cooperation, empathy, engagement, and self-control. Irritability was measured using the Affective Reactivity Index (ARI).
Results: Medium and high, but not low, levels of irritability moderated the relationship between social skills and putamen engagement while adolescents anticipated social evaluation from unpredictable peers. For youth with low irritability, social skills were unrelated to putamen activation when anticipating unpredictable peer feedback (n=18; $p=0.598$). However, for more irritable youth, there was a positive relationship between social skills and activity in left putamen (n=13; $p<0.001$).
Conclusions: This suggests that striatal engagement in unpredictable social contexts may promote adaptive social behavior in irritable adolescents who may otherwise suffer from social impairment.
Supported By: RO1
Keywords: Irritability, Social Functioning, Adolescence, Neuroimaging

F97. Late Chronotype is Associated With Enhanced Amygdala Reactivity and Reduced Fronto-Limbic Functional Connectivity to Fearful Versus Happy Facial Expressions

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Background: Evidence suggests late chronotype individuals are at increased risk of developing depression. However, the underlying neural mechanisms that confer risk are not fully understood.
Methods: Fifty healthy, right-handed individuals without a current or previous diagnosis of depression, family history of depression or sleep disorder underwent functional magnetic resonance imaging (fMRI). Participants completed an implicit emotion processing task (gender discrimination) including happy and fearful facial expressions. Linear effects of chronotype on BOLD response in bilateral amygdala were tested for significance using nonparametric permutation tests. Functional connectivity between amygdala and prefrontal cortex was investigated using psychophysiological interaction (PPI) analysis.
Results: A significant negative correlation between BOLD response and chronotype was observed in bilateral amygdala where late chronotype was associated with an enhanced amygdala response to fearful vs. happy faces (Left: xyz=-30, -6, -18, t=3.97, 198 voxels, $p<0.001$). This response remained significant after sleep quality, age, gender, mood, and time of scan were included as covariates in the regression model. Late chronotype was also significantly associated with reduced functional connectivity between amygdala and dorsal anterior cingulate cortex (dACC) (xyz=4, 26, 22, t=4.53, 54 voxels, $p=0.026$).
Conclusions: The current results appear consistent with theories of impaired emotion regulation of the limbic system (particularly the amygdala) associated with depression. These findings could be related to the 'chronic social jet lag' late chronotypes often experience and may, in part, explain their increased vulnerability for depression. The present findings highlight important clinical and theoretical implications for the prevention and treatment of depression in this at-risk group.
Supported By: University of Roehampton
Keywords: Chronobiology, Brain Imaging, fMRI, Emotion Regulation, Amygdala, Major Depression

F98. Stimulation of Drd1 Expressing Principle Neurons in the Prefrontal Cortex Produces Rapid and Long-Lasting Antidepressant Effects and is Necessary for the Response to Ketamine

Brendan Hare[1], Rong-Jian Liu[1], Ryota Shinohara[1], Ralph DiLeone[1], and Ronald Duman[1]

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Background: Medial prefrontal cortex (mPFC) activity is necessary for the rapid antidepressant effects of ketamine. The mPFC is comprised of multiple pyramidal neuron subtypes but their individual role in the antidepressant response in unclear. The current study addresses this issue using transgenic mice that express Cre recombinase under the control of the dopamine Drd1 or Drd2 promoters to target viral constructs to pyramidal neuron subtypes in an attempt to elucidate their role in rapid antidepressant responses.
Methods: Male and female mice (Drd1cre, Drd2cre) underwent Cre-dependent channelrhodopsin or archaerhodopsin placement into the mPFC prior to optogenetic manipulation

and behavioral testing. Testing included the forced swim test (FST), elevated plus maze (EPM), and novelty suppressed feeding test (NSF).
Results: Stimulation of mPFC Drd1 neurons produced an antidepressant response in the FST 24 hours after stimulation ($p=.02$, $n=9$-11) that lasted up to 7 days ($p=.02$, $n=7$); Drd1 stimulation also produced anxiolytic responses in the EPM ($p=.02$, $n=9$-11) and NSF tests ($p=.03$, $n=7$). In contrast there were no behavioral effects after optogenetic stimulation of the Drd2 pyramidal cell population ($n=7$-9). Importantly, Drd1 inhibition also blocked the antidepressant effects of ketamine administration in the FST and NSF tests ($n=8$/group).
Conclusions: Our results demonstrate stimulation of the Drd1 expressing pyramidal neurons in the mPFC is sufficient to produce rapid and long-lasting antidepressant responses and is necessary for the actions of ketamine. This work will be influential in guiding future cell type specific manipulations to better understand the neurobiology of rapid antidepressant responses and for the development of novel therapeutic agents.
Supported By: RO1 MH093897; RO1 MH105910; Connecticut Mental Health Center, Yale School of Medicine
Keywords: Ketamine, Depression, Medial Prefrontal Cortex

F99. Serotonin Deficiency in the Central Nervous System Alters Epigenetics Mechanisms During Brain Development and at Adulthood

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Background: Dysregulation of central serotonergic system may contribute to the pathophysiology of mood disorders. The recent animal model of rats deficient in tryptophan hydroxylase 2 (TPH2), the rate limiting enzyme of serotonin synthesis in the central nervous system, is an efficient tool to investigate whether a vulnerable genotype can be associated with brain pathology.
Methods: Female and male TPH2 deficient (KO) rats were generated using zinc-finger nuclease technology. Molecular analyses were conducted with real time PCR in the frontal lobe (FL) and hippocampus (H) at postnatal day (PND) 1 while in prefrontal cortex (PF) and dorsal hippocampus (DH) of adult rats. Data were analyzed with unpaired Student's T-test.
Results: Focusing on epigenetic mechanisms, we found an overall decrease of the expression of the histone deacetylase 1 (HDAC1) in male TPH2 KO rats compare to wild type (WT) both at PND1 (FL: -25%, $p<0,05$ vs WT; H: -44%, $p<0,05$ vs WT) and at adulthood (DH: -12%, $p<0,05$ vs WT). Moreover, the expression of the demethylase Gadd45β is the most influenced by serotonin deficiency in female rats (FL: -58% $p<0,01$ vs WT; H: +72%, $p<0,05$ vs WT; PF: +90%, $p<0,01$ vs WT; DH +39%, $p<0,05$ vs WT). Finally, we observe a reduction of HDAC2 mRNA levels in the male hippocampus at PND1 (H: -44% vs WT), and of DNMT1 in the female HD (-12%, $p<0,05$ vs WT).
Conclusions: In summary, our results suggested that the pathological phenotype induced by serotonin deficiency may be due to epigenetic modifications that develop early in life and last a lifetime.
Keywords: Serotonin, Epigenetic, TPH2 ENZYME, Histone Diacetylase

F100. HDAC2 Modulates Behavioral Response to Chronic Stress Through Glucocorticoid Receptor

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Background: A growing body of evidence suggests that aberrant neuroendocrine system and altered epigenetic regulation of gene expression in the brain contribute to the key underlying mechanisms for depression. However to date, it has remained unclear whether aberrant neuroendocrine system in depression is associated directly with altered epigenetic regulation of gene transcription within the brain and subsequent depressive behavior. The aim of the present study is to clarify the molecular mechanisms underlying the susceptibility and adaptation to chronic stress in terms of the interaction of neuroendocrine and gene expression system.
Methods: We used stress-vulnerable BALB/c (BALB) and stress-resilient C57Bl/6J (B6) mice and characterized neuroendocrine, molecular, and behavioral effects of chronic stress episode.
Results: We found increased functioning of glucocorticoid receptor (GR) in the nucleus accumbens (NAc) of stressed BALB but not B6 mice. In addition, both the adrenalectomized and the treatment with GR antagonist prevented chronic stress-induced depression-like behavior in BALB mice. We also found increased recruitment of GR-HDAC2 complexes on the glial cell line-derived neurotrophic factor (Gdnf) gene in stressed BALB but not B6 mice. This aberrant molecular event observed in stressed BALB mice was disrupted by adrenalectomy, suggesting that stress-elicited GR activation could result in HDAC2-mediated epigenetic suppression of Gdnf gene.
Conclusions: We propose that epigenetic regulation of Gdnf gene by HDAC2-GR complexes contributes to the level of susceptibility and adaptation ability of individuals to chronic stressful life events.
Supported By: CREST-JST; KAKENHI (15K09807)
Keywords: Chronic Stress, Epigenetics, Glucocorticoid Receptor, Depression, HDAC

F101. Animal Models of Mood Disorders and the Evaluation of Probiotics

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Background: The contribution of gut microbiota to psychiatric disorders suggests new avenues for treatment. Probiotics are

being evaluated for improving behavioral and/or cognitive abnormalities in patients. However, the effects of probiotics on neurobehavioral changes produced by genetic risk factors have not been evaluated.
Methods: Male and female mice that express truncated human Disrupted-in-Schizophrenia-1 (mutant DISC1), selectively in astrocytes and their littermate controls were treated with placebo or probiotics (lactobacillus and bifidobacteria, 10x9 CFU/mouse) preparations p.o. for 4 weeks. After treatment baseline anxiety- and depression-related behaviors in mutant DISC1 mice were evaluated.
Results: Mutant DISC1 mice (n=8-11 mice per group) exhibited anxiety in elevated plus maze (EPM) and increased immobility in the forced swim test (FST) (all ps$<$0.05 vs. control animals). While effects of the treatment on anxiety were modest (p$>$0.05), increased immobility in FST in mutant DISC1 mice was significantly decreased by the treatment independent of sex (p$<$0.05 vs. mutant DISC1 mice treated with the placebo after ANOVA-detected main effects). In control mice, the treatment did not significantly alter the baseline behaviors. No effects of probiotics preparation were seen on locomotor activity or amphetamine-induced hyperactivity. Analyses of gene expression in the hippocampus and peripheral inflammatory markers are being studied and will be presented.
Conclusions: Our study is the first one to demonstrate the efficacy of probiotics in treating abnormal behaviors in genetically modified mice. This pre-clinical study is consistent with the on-going clinical study that shows that the same probiotics preparation reduces the rate of re-hospitalization in patients with mania.
Supported By: The Stanley Medical Research Institute
Keywords: Anxiety Disorders, Depressive Symptoms, DISC1, Treatment, Microbiome

F102. Human Experimenter Sex Modulates Mouse Behavioral Responses to Stress and to the Antidepressant Ketamine

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Background: Lack of replicability of experimental results may be due to unexpected experimental variables that are not appropriately controlled in experiments. Rodents can differentiate the sex of human experimenters, which may affect their behavioral responses.
Methods: We investigated experimenter sex effects on stress-induced behaviors in mice, and the reversal of such behaviors by the antidepressant drug ketamine. We also investigated the effects of experimenter sex on brain activity following ketamine administration using assessment of quantitative cortical electroencephalography (EEG).
Results: Female—compared to a male—experimenters conducting procedures induced resilience to anhedonia following chronic social defeat stress (CSDS) and development of helpless behavior following inescapable shocks, and resulted in a decrease in immobility time in the forced-swim test (FST). Male-administered ketamine reversed CSDS-induced anhedonia, reduced escape failures following inescapable shock training and decreased immobility time in the FST, while antidepressant responses were absent when a female experimenter administered ketamine. Ketamine administration by female experimenters decreased alpha EEG power. Similar experimenter sex-dependent effects were identified with ketamine's active metabolite (2R,6R)-hydroxynorketamine, but not with other antidepressants or NMDAR antagonists. The nearby presence of a female experimenter was sufficient to block antidepressant actions of male-administered ketamine. Elimination of human volatile odorants precluded antidepressant actions regardless of experimenter sex.
Conclusions: These findings demonstrate the importance of experimenter gender to the outcome of behavioral assessments and antidepressant response to ketamine. Our data argue that the sex of the experimenter may affect replicability within and between laboratories, and should be considered as an important experimental variable.
Keywords: Ketamine, Hydroxynorketamine, Replication, Stress, Depression

F103. Reduced Extent of Myelin Basic Protein Immunoreactivity in Rat Prelimbic and Orbitofrontal Cortices After Chronic Unpredictable Stress and its Correlation With Connexin 43 and Connexin 30

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Background: Astrocytes and oligodendrocytes are pathologically altered in dorsolateral prefrontal and orbitofrontal (OFC) cortices in major depressive disorder (MDD). In rat models of stress (major MDD risk factor) astrocyte gap-junction protein connexin 43 (Cx43) is reduced in the prelimbic cortex (PLC). However, it is unknown whether stress-related changes in Cx43 or in another major astrocyte connexin, Cx30, occur in the rat OFC, or whether PLC and OFC connexin changes correlate with disturbances in myelination.
Methods: Frozen sections containing PLC and OFC of rats after 28 days of chronic unpredictable stress (CUS) and controls (n=6/group) were immunolabeled for Cx43, Cx30 and myelin basic protein (MBP). Density of Cx43 or Cx30 immunoreactivity or the area fraction of MBP immunoreactivity were measured in rat PLC and OFC with StereoInvestigator and ImageJ, and results analyzed with T-test or Pearson correlations.
Results: Density of Cx43-positive puncta in OFC was significantly lower in CUS-treated than in control rats, and Cx30-positive structures were unchanged in PLC. Area fraction of MBP immunoreactivity was significantly lower in PLC and OFC of CUS animals as compared to controls. Density of Cx43-positive puncta and MBP area fraction were positively correlated in PLC and OFC.
Conclusions: Low OFC Cx43 after CUS in rats supports that reduced density of Cx43-positive gap-junctions may be generalized in the prefrontal cortex, but the reduction does not

affect density of Cx30 puncta. The correlation between Cx43- and MBP-immunolabeled structures is consistent with a mechanistic connection between changes in gap-junction protein Cx43 and disturbed myelin maintenance in depression.
Supported By: NIMH grant R56MH113828; Animal Behavior and Imaging Cores of NIGMS grant P30GM103328; IRSP grant from the University of Mississippi Medical Center.
Keywords: Chronic Stress, Depression, Astrocytes, Myelin, Gap Junctions

F104. Sleep Fragmentation and OLF Level in Sodium Pump Alpha-2 Knockout Mice

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Background: Manic patients appear to have a reduced need for sleep. Sleep loss can trigger symptoms of mania or hypomania in bipolar patients. We have reported that mania is characterized by significantly lower endogenous ouabain-like factor (OLF), and bipolar subjects are less able to upregulation of OLF associated with intense exercise. Sodium pump alpha-2 knockout mice have been demonstrated as a purported animal model of mania. This study investigated the relationship of sleep deprivation and OLF level in sodium pump alpha-2 knockout mice.
Methods: Alpha-2 knockout and wild-type Black Swiss mice were used and sleep fragmentation administrated by the moving bar method for 3 days. Sleep fragmentation was performed in the same room as non-sleep deprived mice. Serum was obtained immediately after completion of a trial. OLF was measured by HPLC-RIA.
Results: The baseline of OLF level is significant higher in sodium pump alpha-2 knockout mice compare to wide-type mice (0.82 ± 0.22 nM vs 0.26 ± 0.02 nM, $p=0.03$). The significant elevation of OLF level in wild-type mice after 3 days sleep deprivation (0.53 ± 0.08 nM sleep deprivation vs 0.26 ± 0.02 nM baseline, $p=0.04$). There is no change of OLF level in sodium pump alpha-2 knockout mice after 3 days sleep deprivation (0.60 ± 0.07 nM sleep deprivation vs 0.82 ± 0.22 nM baseline, $p>0.05$). There is no difference of OLF level between male and female mice in both knockout and widetype mice.
Conclusions: Sodium pump alpha-2 knockout mice are abnormal with OLF level and regulation. Sleep deprivation is associated with the elevation of OLF in wide-type mice.
Keywords: Sodium Pump, Sleep Deprivation, Ouabain-Like Factor, Sodium Pump alpha-2 Knockout Mice

F105. Vicarious Defeat Stress-Induced Social Dysfunction is Ameliorated by Ketamine and Chlordiazepoxide in Female C57BL/6 Mice

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Background: Stress is a prevailing risk factor for mood-related illnesses, wherein women represent the majority of those afflicted with major depression. Despite the growing literature suggesting that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains understudied in females at the preclinical level. Thus, the objective of the current investigation was to examine whether exposure to emotional/psychological stress (ES) mediates depression-related outcomes in female mice.
Methods: Female C57BL/6 mice (8-week old, nullparity) vicariously experienced the defeat bout of a male conspecific, by a male CD1 aggressor, for 10 consecutive days. Twenty-four h after the last stress exposure, female mice were tested in the social interaction test. Furthermore, we examined whether ketamine and chlordiazepoxide, pharmacological agents used to treat mood-related disorders in the clinical population, would reverse the ES-induced social dysfunction.
Results: When compared to controls, female mice exposed to ES displayed decreased social behavior, 24 hr post stress exposure. Also, they displayed higher levels of blood serum corticosterone, as well as decreased body weight. Lastly, the ES-induced avoidance-like phenotype was rescued by both ketamine and chlordiazepoxide.
Conclusions: Our data indicate that female mice exposed to ES display a behavioral- and physiologic-profile that mimics symptoms of depression in the clinical population. As such, this experimental model may be adopted to examine vicarious stress-induced mood-related disorders, as well as pharmacological therapeutic response, in a sex specific manner.
Supported By: SC2GM109811
Keywords: Social Defeat Stress, Females, Psychological Stress, Ketamine, Depression

F106. The Lonely Mouse: A Model for Studying Maternal Psychological Stress and its Consequences in the Offspring

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Background: It is well established that antenatal maternal psychopathology has long-term consequences on the offspring's wellbeing and mental health. To date, models that investigate this association rely mainly on exposure to chronic or acute unpredictable stress during pregnancy, which is often based on physical stressors characterized by medium translational value. Therefore, we propose the use of psychosocial stress, in the form of social isolation-rearing, to investigate the effects of antenatal maternal stress on the offspring.
Methods: C57BL/6 female mice were socially isolated, or group housed, from weaning to adulthood and subjected to behavioural testing to confirm the development of a depressive-like phenotype. A subgroup of animals was treated with Fluoxetine (10mg/kg) for the last 3 weeks of social isolation, pregnancy and weaning. All the animals were mated and the offspring were subjected to cognitive and behavioral testing in adulthood.

Results: Social isolation rearing induced weight gain, basal plasma corticosterone reduction and depressive-like behaviours. Both female and male offspring of socially isolated mothers displayed increased anxiety and altered fear expression. Male offspring also presented metabolic alterations and cognitive deficits. Prenatal fluoxetine was effective in rescuing some of the above-mentioned behavioural abnormalities but detrimental for others.
Conclusions: Our results demonstrate, for the first time, that social isolation rearing preceding pregnancy is sufficient for inducing long-term behavioural and metabolic alterations in the offspring. The social isolation-rearing model thus offer a translationally-relevant setting in which to further investigate the mechanisms underlying the association between prenatal stress and psychopathology in the offspring, and the contribution of pharmacological treatments.
Keywords: Depression, Anxiety, Social Isolation, Behavior, Animal Models

F107. The Molecular Pathways in the Dentate Gyrus and Blood Underlying Poor and Good Antidepressant Treatment Response

David Herzog[1], Hyobin Jeong[2], Diego Pascual Cuadrado[1], Michael van der Kooij[1], Tanja Jene[1], Verena Opitz[1], Amitava Basu[2], Vijay Tiwari[2], and Marianne Müller[1]

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Background: There are currently two major challenges in the treatment of major depression, calling for innovative research approaches: 1. the absence of biomarkers predicting antidepressant response and 2. the lack of conceptually novel antidepressant compounds.
Methods: Male, adult DBA/2J mice show high innate anxiety and are suitable to model heterogeneity in response to antidepressant treatment. To identify region-specific putative novel targets mediating response to antidepressant treatment, mice were treated for 14 days orally with either paroxetine or vehicle. Efficacy of antidepressant treatment was assessed using the Forced Swim Test. For the identification of peripheral biosignatures predicting response, we collected blood samples at baseline and following 14 days of treatment (longitudinal design), whereas for the identification of novel antidepressant targets, we specifically dissected the hippocampal dentate gyrus using a microdissecion protocol for native hippocampal tissue. We extracted stranded total RNA from samples and sequenced.
Results: Paroxetine treatment induced antidepressant-like ($p<0.0001$) and anxiolytic ($p=0.0496$) behavioral effects. 112 genes were differentially regulated by paroxetine treatment in the hippocampal dentate gyrus, among them neurogenesis-related genes like Satb2 and Pou3f1. Hindbrain development, and neuron projection development were enriched biological processes based on GO-term analysis. 394 genes in blood and 529 genes in dentate gyrus samples were differentially regulated, when stratifying the animals according to their response status. Cell cycle, neuropeptide signaling pathway, and synaptic transmission were enriched biological processes.
Conclusions: With this study we provide additional strong evidence that neurogenesis plays a crucial role in mediating antidepressant treatment effects and might determine the response status in rodents.
Supported By: Mainz Research School of Translational Biomedicine
Keywords: Major Depressive Disorder (MDD), Predictive Biomarkers, Neurobiology, Translational Research, Antidepressant Response

F108. Plasma TNF-Alpha is Associated With Stressful Life Events in Youth With Bipolar Disorder

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Background: Immune dysfunction (with associated elevation in levels of inflammatory cytokines) has been implicated in Pediatric Bipolar Disorder (PBD). Early life stress has also been associated with elevated levels of proinflammatory cytokines. In the present study we evaluated the association of stressful life events and TNF-α in youths with Bipolar Spectrum Disorders (BSD).
Methods: 16 youths with BSD (7-17 years inclusive) were recruited. The diagnosis of BSD was done with the Mini International Neuropsychiatric Interview (Mini) – KID Client version 7.0 for the youth. The MINI – KID 7.0 Parent version was used to interview parents about their child's diagnoses. The youths also completed the age-appropriate Stressful Life Events Schedule (SLES). ELISA was performed on fasting plasma to measure TNF-α. Pearson correlation was used to evaluate the association of TNF-α and SLES scores.
Results: TNF-α positively correlated with SLES scores ($r=0.55$, $p=0.027$).
Conclusions: Our results are consistent with previous studies that have associated stressful life events with proinflammatory cytokines. Studies comparing immune response to stressful life events in youths with BSD vs. healthy control youths will confirm whether cytokine-related stress reactivity can be utilized as a biomarker in youths with BSD.
Supported By: The John S Dunn Foundation
Keywords: Bipolar Disorder, Proteomics, Biomarkers, Youth, Mood Disorders

F109. Developmental Effects on Implicit Associations to Suicide: Preliminary Data From a Multi-Site Study

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Background: Behavioral markers of acute suicide attempt risk are a guide to underlying biology but may be affected by age. While some studies in younger samples have found that the Implicit Association Test (IAT) using death and suicide-related words identifies or even predicts suicide attempt risk, it is unclear if these effects extend to older adults. Preliminary data from an ongoing, multisite, lifespan study of neurocognitive factors in suicidal behavior examined whether suicide attempters' rapid self-attributions to suicide can be replicated and extend through adulthood.
Methods: 68 past suicide attempters in a current depressive episode, 55 depressed patients with no suicide attempt history, and 85 healthy volunteers ranging in age from 16 to 80, recruited from medical centers in New York, Pittsburgh, and Columbus, Ohio were compared on IAT performance.
Results: There were no simple group differences on the IAT difference score, however significant age effects were found. ($r = -.46$, $p < .001$). Moreover, a significant group by age interaction was found ($p = .02$), such that past attempters showed a stronger association to death and suicide in adolescence and early adulthood, but not in later adulthood. Age was not associated with depression severity in patients ($r = -.08$, $p = .39$) or with severity of attempt in attempters ($r = .17$, $p = .16$).
Conclusions: This the first study to demonstrate age effects on the suicide IAT, and developmental limitations on the IAT's ability to discriminate suicide risk. IAT effects diminish by later adulthood, possibly due to relative slowing of self-attributions toward death at older ages.
Supported By: American Foundation for Suicide Prevention
Keywords: Suicide Risk Factors, Depression, Brain Development and Aging

F110. Assessment of Neurocognitive Function in Individuals With Treatment-Resistant Depression Undergoing a Ketamine Trial

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Background: Recent evidence has shown that ketamine has rapid antidepressant effects in patients with treatment resistant depression (TRD). However, there has been little research on the effects of repeated ketamine infusions on cognition.
Methods: This neurocognitive study took place during a single-centre randomized controlled trial of ketamine. Participants with TRD ($N = 38$) underwent cognitive assessments before and after receiving a total of 7 ketamine infusions. The cognitive battery measured global cognitive function (Modified Mini Mental State Exam [MMSE]), processing speed and executive function (Trail Making Tests A and B [TMT-A, TMT-B]), attention and working memory (Digit Span [DS]), verbal learning and memory (California Verbal Learning Test [CVLT-II]), and autobiographical memory (Autobiographical Memory Interview-Short-Form [AMI-SF]). Depression severity was evaluated with the Montgomery-Åsberg Depression Rating Scale (MADRS).
Results: Overall, 56% of participants met antidepressant response criteria after repeated ketamine infusions (50% decrease in MADRS scores). When adjusted for change in depressive symptoms, repeated measures ANOVAs revealed no significant changes in participants' cognitive scores before and after repeated ketamine infusions (MMSE, $p = .14$; TMT-A, $p = .84$; TMT-B, $p = .11$; DS total, $p = .78$; CVLT-II learning, $p = .34$, CVLT-II short-delay, $p = .48$; CVLT-II long-delay, $p = .88$; AMI-SF, $p = .26$).
Conclusions: Repeated ketamine infusions did not have any short-term adverse neurocognitive effects on individuals with TRD. Future studies are required to examine if any long-term cognitive impacts from ketamine treatment exist.
Supported By: Canadian Institutes of Health Research (CIHR)
Keywords: Neurocognition, Ketamine, Major Depressive Disorder (MDD), Treatment-Resistant Depression

F111. Multiple Pathways to Suicidal Behavior: Genetic and Neurocognitive Differences Between Suicide Attempters With High and Low Aggression-Impulsivity and Non-Attempters

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Background: Suicidal behavior is a complex phenomenon, likely to be associated with different pathways. We tested whether attempters with high vs. low aggression-impulsivity scores differed from non-attempters on genotype or neurocognitive deficits.
Methods: 243 attempters, 320 depressed non-attempters and 148 healthy volunteers were genotyped using the Illumina Addiction Array. Among suicide attempters, a mixture distribution model identified two components on an aggression, impulsivity and hostility factor that was age- and sex-adjusted, attempters were thus split into high and low aggressive-impulsive subtypes. SNP-wise logistic regression tested differences in genetic variants for each subtype vs. non-attempters. 330 subjects underwent

neurocognitive testing and scores were compared by group using ANOVA.
Results: Lethality of attempts did not differ by subtype ($p=0.330$), high-aggression attempters had higher subjective, but not objective, depression ($p<0.001$). Significant SNPs ($p<0.005$) for the high-aggression attempters subtype vs. non-attempter comparison were on the neurotensin receptor (NTSR1), serotonin transporter (SLC6A4) and tachykinin precursor (TAC1) genes, for the low-aggression attempter subtype on cholecystokinin receptor (CKBR), serotonin 2A receptor (HTR2A), mu opioid receptor (OPRM1) and alcohol dehydrogenase (ADH7). The high aggression subtype had worse working memory scores as measured on the A not B test ($p=0.016$) and Buschke Long-Term Retrieval Score ($p=0.025$) compared to non-attempters, while the low aggression subtype had worse Benton Visual Retention scores ($p<0.001$), both subtypes had worse Stroop interference score ($p=0.003$).
Conclusions: Highly aggressive-impulsive attempters' suicidal behavior may be associated with specific genotype variants connected to stress response and inflammation, and also with working memory deficits, while attention deficits may be shared with other subtypes.
Keywords: Suicide Attempts, Cognitive Deficits, Genetic Association, Impulsive-Aggresive, Working Memory

F112. Association Between Hypovitaminosis D and Cognitive Inhibition Impairment During Major Depression Episode

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Background: Major depressive episode (MDE) has been associated with cognitive functioning alteration and hypovitaminosis D (hypoVD), but the relationship between hypoVD, depression, and cognition is not well understood. We aimed to compare patient with MDE with or without hypoVD in regard of cognitive functioning.
Methods: 91 patients (38.5 years old, 65.9% female) with MDE were included in a cross-sectional study and were evaluated with a complete cognitive battery. None of the participants were medicated at the inclusion. Serum 25-hydroxyvitamin D was measured using LC-MS/MS method, and hypovitaminosis was defined as 25OHD $<$50nmol/L. Covariates were gender, season of dosage, first MDE onset, age, body mass index and depression severity
Results: Patients with hypoVD demonstrated a higher stroop interference index time underscoring that means low cognitive inhibition ability. Multiple logistic regression confirmed that hypoVD was significantly associated with high stroop interference time index after controlling by gender, season of dosage, first MDE onset, age, body mass index and depression severity.
Conclusions: Our results suggest that patient with MDE having hypoVD may be more prone to cognitive impairment.
Keywords: Vitamin D, Depression, Stroop, Cognitive Inhibition

F113. Hippocampal Connectivity Insulates High-Risk Adolescents From the Relationship Between Stress and Depressive Symptoms

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Background: Stress is a significant causal agent in the development of anxiety and depression. In addition, chronic and acute stress result in the stimulation of the hippocampus, and patients with a history of depression show clear deficits in hippocampal structure and function. However, much less is known about the relationship of stress to hippocampal connectivity, and how these network relationships contribute to the emergence of depressive outcomes in adolescents.
Methods: We were interested in how familial risk for depression might influence the relationship between the frequency of stressful life events (Stressful Life events Schedule - SLES), depressive symptoms (Mood and Feelings Questionnaire - MFQ) and hippocampal connectivity. Longitudinal data were collected from 320 adolescents who were recruited as part of a study designed to investigate factors contributing to risk for depression. Participants were high- and low-risk adolescents scanned and assessed at baseline (mean age = 13.6) and a 2-year follow-up, using diffusion-weighted imaging tractography, which allows for of white matter pathways connecting the hippocampus.
Results: We found a significant risk group x SLES x hippocampal connectivity interaction, such that MFQ was sensitive to SLES in low-connectivity, high-risk adolescents, in contrast, high-connectivity, high-risk adolescents did not show increases in depressive symptoms with increasing stress.
Conclusions: These findings suggest that connectivity helps to insulate developing adolescents from the negative effects of stress, and help to clarify the neural mechanisms that may underlie the emergence of adolescent depression.
Supported By: NIAA R01AA016274
Keywords: Brain Connectivity, Adolescent Depression, Diffusion Tensor Imaging (DTI), Early Life Stress

F114. Feature-Based Selective Attention as a Biomarker of Impaired Cognition in Depression

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Background: Concentration impairments are a hallmark of many psychiatric illnesses, and are included as diagnostic criteria for Major Depressive Disorder (MDD). Although MDD patients have been shown to have particular impairments in tasks requiring feature-based selective attention (e.g., Stroop

task), detailed characterization of these impairments and their neural circuit basis remains limited.
Methods: We used multi-modal testing to characterize attention impairments in a large sample of un-medicated patients (n = 1008) and healthy controls (n = 336) from the international Study to Predict Optimized Treatment – Depression (iSPOT-D), of whom 15% also underwent magnetic resonance imaging. We investigated relations between behavioral performance assessed by computerized tests, symptom severity, and hippocampal volume quantified using voxel-based morphometry.
Results: Depressed patients performed worse than healthy controls on the Stroop task, reporting word names more slowly (bootstrapped 95% CIs (1013, 1049) and (1072, 1107), respectively). This poorer Stroop performance was associated negatively with both left and right hippocampal volume in patients ($r(87) = -0.28$, $p < .01$) but not controls ($r(38) = 0.06$, $p = .74$). In patients, this effect was independent of overall symptom severity ($r(574) = 0.04$, $p = 0.38$) and specific sleep problems ($F(2,612) = 3.23$, $p < .05$).
Conclusions: Impairments of feature-based selective attention may be associated with altered hippocampal volume related to stress hyper-reactivity. Further characterization of heterogeneous attention impairments may reveal insights into the underlying neurobiology of depression and help develop biomarkers for interventions targeting cognition.
Supported By: NDSEG, Brain Resource
Keywords: Attention, Depression, Hippocampus, Stroop, iSPOT-D

F115. CANTAB (Cambridge Neuropsychological Test Automated Battery) Reveals Impaired Sustained Attention in Offspring of Bipolar Parents

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Background: Bipolar disorder (BD) is mainly characterized by dramatic mood shifts due to a biased process of emotional information. An overlooked aspect of BD is the potential development of cognitive deficit amongst various cognitive domains that have the influence on the course of illness. We used Cambridge Neuropsychological Test Automated Battery (CANTAB) to analyze if a group of Bipolar Offspring (BPO) shows any trait of deficit compared to healthy controls (HC).
Methods: 26 participants (age 7-17 years inclusive; 10 bipolar offspring and 16 healthy controls) were enrolled in an outpatient specialty mood disorders clinic. CANTAB cognition test battery was administered with desired modules. The rapid visual processing (RVP) task is a measure of attention and psychomotor speed. We used ANCOVA to compare results of different cognitive tests between groups while adjusting for age and sex.
Results: The RVP mean latency ($p = 0.321$) was significant between HC and BPO. Compared to HC, bipolar offspring have a longer response time, therefore showing lower sustained attention span.
Conclusions: Preliminary data reveals early evidence of cognitive function deficit in the BPO group by means of lower sustained attention tendency when compared to HC. Impaired sustained attention can serve as a biological marker for prodromal diagnosis and improved prognosis. Such impairments can be a candidate for biological trait markers of the disorder and stage-specific changes could predispose them to develop the disorder. Further studies are necessary to see the neural underpinnings of this tendency in BPO.
Supported By: The John S. Dunn Foundation
Keywords: Bipolar Disorder, Neurocognition, Bipolar Offspring, Mood Disorder, Sustained Attention

F116. A Preliminary Evaluation of Nicotine's Impact on Functional Connectivity in Major Depressive Disorder

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Background: Individuals with Major Depressive Disorder (MDD) have decreased coupling between the salience network (SN) and central executive network (CEN). This reduced coupling may result in ineffective switching into CEN-dominated states such as those requiring external focus. Nicotine may ameliorate this deficit as nicotine enhances the reduced SN-CEN coupling noted in nicotine dependent smokers going through nicotine withdrawal.
Methods: To determine the impact of nicotine on SN-CEN coupling, we administered 2mg of nicotine or placebo to non-smokers with MDD (n = 18) and healthy controls (HCs; n = 17). Study drugs were administered in a double-blind, randomized, cross-over design prior to resting state functional magnetic resonance imaging. Network time course cross-correlations were compared between groups and drug conditions.
Results: A significant group by drug interaction was observed for SN-LeftCEN coupling, $F(1,33) = 4.50$, $p = .042$. Specifically, acute nicotine reduced SN-LeftCEN coupling in MDDs, $t(33) = -2.10$, $p = .043$, compared to HCs. MDDs but not HCs showed significantly lower SN-LeftCEN coupling values on nicotine compared to placebo, $t(17) = -2.58$, $p = .020$.
Conclusions: Contrary to our hypothesis, MDDs showed no SN-CEN coupling deficit on placebo, but reduced SN-CEN coupling following nicotine administration. This finding may be explained by the hypercholinergic hypothesis of depression. It is plausible that nicotine's influence on SN-CEN coupling follows an inverted-U shape with nicotine normalizing SN-CEN coupling when acetylcholine is low, but disrupting coupling at higher cholinergic states.
Supported By: K01DA029645; K02DA042987
Keywords: Resting State Functional Connectivity, Major Depressive Disorder (MDD), Nicotine

F117. Early Detection and Intervention for Mood Disorders: A Pilot Study

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Background: We recently began a pilot study to evaluate the mental health climate at UC San Diego and assess the need for an early detection and intervention program. Another goal of this study is to develop a risk prediction model for mood disorders based on the behavioral, environmental, and genetic data to identify students at risk prior to the onset of symptoms.
Methods: In total, 143 students completed an online, anonymous survey during the spring and summer of 2017 with another 200 in process. The survey used the Patient Health Questionnaire to screen for depression, the Mood Disorder Questionnaire to screen for bipolar spectrum disorders, and the Suicide Behaviors Questionnaire-Revised to screen for suicide risk. Additional questions were included to inform lifetime diagnoses of major depression and bipolar disorder according to DSM criteria. The remainder of the survey evaluated potential behavioral, environmental, and genetic risk factors.
Results: Initial analyses revealed that 69% of respondents had experienced significant symptoms of depression and/or mania. Of these students, 64% had current symptoms, 32% were abusing drugs and/or alcohol, and 16% were at high risk for suicide. Applying DSM criteria, 24% of respondents appeared to meet criteria for a mood disorder. Of these students, only 31% had been previously diagnosed, and less than half had utilized campus mental health services.
Conclusions: These initial results suggest that current mental health outreach programs have not effectively captured a large portion of students with undiagnosed mood disorder at UC San Diego, highlighting the need for an early detection and intervention program.
Supported By: Philanthropic donation from Mr. Joseph E. Edelman
Keywords: Mood Disorders, Early Risk Detection, Depression, Bipolar Disorder

F118. Risk of Atherosclerotic Cardiovascular Disease in Patients With Bipolar Disorder and Accuracy of a Cardiovascular Risk Calculator

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Background: We aimed to test the association between bipolar disorder (BD) and atherosclerotic cardiovascular disease (ASCVD) and determine if the American College of Cardiology/American Heart Association pooled cohort equation (AHA-PCE) can accurately predict events in BD patients.
Methods: We used the Rochester Epidemiology Project, a community-based cohort of consecutive patients that sought primary care between the years 1998-2000. Inclusion criteria were those of the AHA-PCE. We excluded those with ASCVD, atrial fibrillation or heart failure at baseline. BD diagnosis was validated using DSM-IV criteria. ASCVD events included fatal and nonfatal myocardial infarction and ischemic stroke. We compared calculated and observed 10-year ASCVD risk and calculated cox-proportional hazard ratios.
Results: We included 23,629 adults, mean age±SD 53.8±10.2, 46% males, with a mean follow-up of 16.1± 2.7 years. 1,237 ASCVD events occurred during follow-up in 967 (4.1%) people. 378 (1.6%) patients had BD, age 52.4±9.8, 41% males. BD was not associated with increased ASCVD events (unadjusted HR=1.2 95%CI=0.7-1.8, p=0.4) nor after adjusting for age and gender (HR=1.3 95%CI=0.9-1.8, p=0.1) or AHA-PCE risk (HR=1.2 95% CI=0.7-1.8, p=0.3). AHA-PCE performed well in BD patients (area under the ROC curve (AUC)=0.82, p=<.0001) but slightly overestimated ASCVD events (observed=5% vs predicted=7.9%, p<.0001). Performance was similar in the general population without BD (AUC=0.76, p= <.0001 and observed=4% vs predicted=7.7%, p=0.03); p=0.3 for the comparison of AUC.
Conclusions: In this patient population, BD was not associated with an increased ASCVD event risk. The AHA-PCE has good discriminatory power and slightly overestimates ASCVD risk in people with and without BD.
Supported By: This work was supported in part by the European Regional Development Fund-FNUSA-ICRC (No. Z.1.05/1.1.00/02.0123) by project no. LQ1605 from the national program of Sustainability II (MEYS CR), by the project ICRC-ERA-Human bridge (No.316345) funded by the 7th Framework Programme of the European Union.
Keywords: Bipolar Disorder, Cardiovascular Disease, Cohort Studies

F119. Longitudinal Association Between Depression, Depression Characteristics and Inflammatory Markers: Results From the NESDA Study

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Background: While cross-sectional associations of inflammatory markers interleukin(IL)-6 and C-reactive protein (CRP) with major depressive disorder (MDD) are well established, evidence for longitudinal associations mostly comes from studies on depression symptoms but not diagnoses. The aim of the current study was to explore both cross-sectional associations as well as bi-directional longitudinal associations between depression diagnoses and symptoms with inflammation markers in an adult sample over a 6-year period.

Methods: Data were from the baseline (n=2416) and 2- and 6-year follow-up assessment (n=1925 and n=1924, respectively) of the Netherlands Study Of Depression and Anxiety. CRP and IL-6 were assessed at each wave, as were the CIDI diagnostic interview and Inventory of Depressive Symptomatology. Linear mixed models and GEE models with a binomial distribution were used to study longitudinal associations between depression and inflammation, and vice versa.
Results: There was a consistent cross-sectional association between depressive disorder and symptoms with IL-6 across all follow-ups (Cohen's d depression diagnosis=0.07 (95%CI 0.01-0.012), p=0.017; BIDS(se)=0.0002(0.0001, p=0.016)). IL-6 was also longitudinally associated with depression; higher IL-6 levels predicted subsequent chronic course in those with a diagnosis at baseline (OR =1.08, 95%CI 1.03-1.14), and both depressive disorder and high severity predicted higher IL-6 levels at the subsequent follow-up (p-values<0.01). In contrast, CRP was not associated with current depression in cross-sectional and longitudinal analyses.
Conclusions: In this longitudinal study, both cross-sectional and bidirectional longitudinal associations were found between depression and IL-6 levels. This underlines the importance of targeting inflammation pathways in the treatment of MDD.
Supported By: The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum). Dr. Lamers has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° PCIG12-GA-2012-334065. Data analyses and biomarker assays were partly funded through NWO funding (VICI, Grant No. 91811602) and through grant support from Janssen Research & Development, LLC, Titusville, NJ, USA. Janssen did not have direct access to the data and was not involved in the conduct of the data collection, management and analyses.
Keywords: Inflammation, Major Depressive Disorder (MDD), Longitudinal Cohort, IL-6, C-Reactive Protein

F120. Genome-Wide Analyses of Venlafaxine Response in Late-Life Depression

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Background: Treatment of late-life depression (LLD) with antidepressants is a challenging task until remission is achieved. This genome-wide association study (GWAS) was conducted to identify novel variants associated with remission on venlafaxine treatment in LLD which will help to develop preemptive genetic testing models in the clinic.
Methods: Three-hundred and fifty-four participants (>60 years) of mixed ethnic ancestry, diagnosed with major depression (MADRS>15), were treated with open-label venlafaxine (37.5mg/day, up to 300 mg/day) for approximately 12 weeks. We used the Illumina PsychArray BeadChip which was then imputed to the 1000 Genomes reference panel (Phase 3) using IMPUTE v.2.2. to obtain N = 7,389,525 variants per individual.
Results: Our top hits with MADRS score change were located in variants near MIR1246 ($\beta = 16.98$, $p = 9.22 \times 10\text{-}7$) and in ERBB4 ($\beta = 6.46$, $p = 5.35 \times 10\text{-}7$). ERBB4 which has been implicated in risk for schizophrenia, was also associated with post-ketamine treatment down regulation of GABA and glutamate levels in the rat prefrontal cortex and hippocampus, resulting in an antidepressant effect. We also observed a suggestive association between remission status and a variant in phosphodiesterase gene PDE9A (OR = 6.03, $p = 3.30 \times 10\text{-}6$), suggesting a role in synaptic neurotransmitter signaling. PDE9A has been previously associated with risk for depression in another study.
Conclusions: We found novel gene variant associations with measures of venlafaxine remission in older adults in interesting neuro-relevant genetic pathways. Post-GWAS analyses and integrated machine learning models will be presented to elucidate the biological context and potential clinical implications.
Supported By: NIH
Keywords: Late Life Depression, Antidepressant, GWAS, Pharmacogenomics, Precision Medicine

F121. Investigating Glucocorticoid Receptor Binding in Lymphoblastoid Cell Lines

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Background: The glucocorticoid receptor (GR) is a key regulator of the stress response system. Upon activation, the GR translocates to the nucleus where it regulates the transcription of specific genes. It has recently been demonstrated that functional variants in a subset of these GR target genes are associated with the risk of developing major depressive disorder. Therefore, the first objective of this project is to investigate whether high vs. low genetic risk profiles are associated with differential GR binding, resulting in the dysregulation of the stress response system. In this study, we perform preliminary experiments designed to optimize GR chromatin immunoprecipitation (ChIP).
Methods: To investigate GR binding, GR ChIP sequencing (ChIP-seq) in lymphoblastoid cell lines (LCLs) was used. The

GR was activated by stimulating the cells with its agonist, dexamethasone. To assess enrichment, qPCR was performed using probes for FKBP5, a known target of GR. Sequencing was performed on the HiSeq4000.
Results: Using a specific GR antibody, an IP was performed and a >60 fold enrichment compared to our control IP (IgG) was observed via qPCR. Sequencing identified >2500 peaks and confirmed the success of the GR ChIP, with peaks being observed at GREs in GR targets, such as Per1 and FKBP5.
Conclusions: During this preliminary phase of the project, we successfully optimized the stringent conditions required for GR ChIP. Performing the GR ChIP-seq in LCLs with high and low risk profiles will provide valuable insight into how common genetic variants in GR responsive loci contribute to the development of psychiatric disorders.
Supported By: MPI Psychiatry
Keywords: Glucocorticoid Receptor, Depression, HPA Axis, Polygenic Risk Score

F122. The Neuronal Stem Cell Transcriptome of Premenstrual Dysphoric Disorder

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Background: Premenstrual dysphoric disorder (PMDD) is characterized by recurrent affective and behavioral symptoms during the luteal phase of the menstrual cycle. Clinical studies show that in women with PMDD, symptoms recur after re-exposure to physiologic levels of estradiol (E2) or progesterone (P4) during GnRH-agonist-induced ovarian suppression. Furthermore, women with PMDD show symptom reduction after blocking the conversion of P4 to allopregnanolone (ALLO) across the menstrual cycle.
Methods: Neural stem cells (NSCs) were created from induced pluripotent cell (iPSC) lines from women with PMDD and asymptomatic controls (n=3, 2, respectively; 2 technical replicates per individual). Immunofluorescent staining verified NSC characterization. NSCs were exposed to vehicle (DMSO), E2, P4, or ALLO for 24hrs at 100nM, and examined for gene expression differences via AmpliSeqRNA transcriptome. Analyses were performed with Partek Flow, R, and GSEA.
Results: Unsupervised hierarchical clustering showed diagnosis- and hormone treatment-specific clustering. Gene expression heat maps show differential expression in PMDD NSCs vs controls, as well as between hormones. Pairwise comparisons between NSC samples show a 0.98 mean Pearson correlation coefficient, though only 0.21 when NSCs were compared to their corresponding lymphoblastoid cell line. Top GSEA hits on genes expressed uniquely in NSCs compared to LCLs showed neuronal-specific pathways.
Conclusions: We successfully differentiated neural stem cells from iPSCs, as shown through immunofluorescent staining, r^2 value, and pathway analysis. NSCs from women with PMDD vs asymptomatic controls showed differential gene expression both between diagnosis and in response to hormone. These data suggest that E2, P4, and ALLO might contribute to differential neuronal development involved in PMDD.
Keywords: Human Neural Stem Cells, Transcriptome, Mood Disorders

F123. Genome-Wide Epigenetic Signatures of Major Depressive Disorder in Women

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Background: Major depressive disorder (MDD) is the most prevalent mental disorder, both in the United States and worldwide, where it affects over 350 million individuals. The lifetime prevalence of MDD in women is up to 20%, which is twice that of men. Although epigenetic mechanisms have been implicated in MDD risk, most studies to date have used candidate gene approaches. We conducted what we believe to be the first epigenome-wide association study (EWAS) of MDD in women.
Methods: Our sample included 110 European-American women (55 MDD cases, 54 age-matched controls), with a median age of 43±14.5 yr. DNA was extracted from whole blood samples and EWAS was assessed using the Illumina Infinium HumanMethylationEPIC array. To identify differentially methylated CpG sites, we performed an association analysis using the 'cpg.assoc' function from the minfi Bioconductor R package, adjusting for age, estimates of cell proportions, and the first 10 principal components estimated using the Barfield et al. (2014) method to correct for population stratification.
Results: Association analysis identified a significant differentially methylated CpG site at cg03450102 ($p = 6.1 \times 10^{-8}$, FDR = 0.04), which maps to the exonuclease 1 (EXO1) gene. EXO1 is involved in DNA repair and has been identified in a genome-wide association study (GWAS) of age at menopause.
Conclusions: These results suggest that changes in DNA methylation at EXO1 play a role in MDD in women, but require replication. Two limitations of this study are the modest sample size and the use of blood for DNA extraction to model tissue-specific DNA methylation changes.
Supported By: NARSAD
Keywords: Epigenetics, Depression, DNA Methylation

F124. PPD ACT, an App-Based Postpartum Depression Genetic Study

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Background: Postpartum depression (PPD) is one of the most frequent complications of childbirth (prevalence 10-15%). PPD is suited to genetic investigation as it is more homogenous than major depression outside of the perinatal period (i.e. women of childbearing age exposed to similar biopsychosocial stressor). Therefore, we developed an iOS app (PPD ACT) to recruit women with a lifetime history of PPD to sufficiently power genome wide association studies.
Methods: PPD ACT has two basic components: participant screening for PPD and collection of DNA from cases. Women download the app, complete basic eligibility, and are presented with informed consent. Participants are screened for PPD using the EPDS lifetime version. Cases are invited to participate in DNA collection and sent a spit kit via USPS. Clinical validation was performed in UNC Hospitals and recall validity assessed 6 − 8 months after initial assessment.
Results: PPD ACT was released on March 21, 2016. The data presented are from the US, one year post-launch. 10,473 participants completed phenotyping, with 7,607 PPD cases (3,038 samples biobanked). Lifetime EPDS threshold for case status was $\geq$ 13 with the median score for cases was 23 (IQR: 20 − 25). Sensitivity was 100% in clinical validation (n=43). There was 92% agreement in case status (AC1=0.92, 95% CI: 0.91 − 0.93; n=2,149).
Conclusions: PPD ACT is the first mobile health application for a psychiatric genetics study, screening and collecting samples directly from participants. The response obtained suggests we are on our way to helping women who suffer with PPD.
Supported By: NIMH, Foundation of Hope
Keywords: Postpartum Depression, mHealth, Genetics

F125. Genome-Wide Association Study of Anti-Epileptic Drug Mood Stabilizer Response in Bipolar Disorder Patients

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Background: Anti-epileptic drugs (AED) are a heterogeneous set of medications, some of which demonstrate mood-stabilizing properties in bipolar disorder (BD). However, not all patients with BD respond to AED mood stabilizers (AED-MSs). This study aimed to identify genetic variations associated with response to AED-MSs in BD patients.
Methods: 199 participants from the Mayo Clinic Bipolar Disorder Biobank with a retrospective assessment of drug response (Alda score) for one or more AED-MSs (valproic acid, divalproex, lamotrigine, carbamazepine, or oxcarbazepine) were included in the analysis. For subjects with multiple Alda scores, the medication with the lowest B score was selected. We performed a genome-wide association analysis using the total Alda score as the outcome variable.
Results: Seven SNPs in the thrombospondin type 1 domain containing 7A (THSD7A) gene were associated with response to AED-MSs at a genome-wide significance level (top SNP rs78835388; p=9.1E-9). Other SNPs of potential biological interest with suggestive evidence of association included those located in the vav guanine nucleotide exchange factor 3 (VAV3; p=8.8E-7) and the neurexin 3 (NRXN3; p=1.0E-6) genes.
Conclusions: These preliminary data suggest that THSD7A may contribute to AED-MS response in BD. THSD7A has been reported to be associated with BD, major depression, and autism. Together with the findings in VAV3 and NRXN3, which have also been associated with schizophrenia and BD, our findings suggest that certain genes associated with BD risk may also be important predictors of AED-MS response. These findings warrant replication in a larger cohort.
Keywords: Mood Stabilizers, Bipolar Disorder, Pharmacogenetics

F126. Quantitative Bipolarity and its Heritability

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Background: The search for a genetic basis of bipolar disorder (BP) has been inconclusive. In genetic studies, defining the phenotype by diagnosis may miss risk-allele carriers without BP, wrongly grouping them into control groups. We hypothesize that a quantitative bipolarity assessment may identify a trait that tags BP patients but also those with increased risk for BP, and is still heritable.
Methods: We developed a Quantitative Bipolarity Scale (QBS) and administered it to a sample of Old Order Amish/Mennonite [n=311 (n=20 BP, n=62 Major Depressive Disorder, n=3 psychotic disorder, n=26 other psychiatric disorders, n=200 controls)]. QBS was compared across diagnosis with oneway ANOVA. Taking advantage of the large pedigrees in these participants, heritability was calculated using the variance components method (SOLAR-Eclipse).
Results: The BP diagnosis was highly heritable (h2=0.71±0.45, p=0.033). The QBS score was higher in BP group compared to all others (p<0.001). There were significant differences between the QBS score in subjects with bipolar (31.5±3.6) compared to depression (16.7±2.0), other psychiatric diagnosis (6.96±1.9), and no psychiatric diagnosis (5.97±0.65) (all p<0.001). QBS in the whole sample was significantly heritable (h2=0.46±0.15, p<0.001). When subjects with psychiatric illness were removed the QBS heritability was similar (h2=0.59±0.18, p<0.001), suggesting QBS is a heritable trait not driven by having BP or a psychiatric condition.
Conclusions: Quantitative bipolarity as measured by QBS can easily separate BP patients from other psychiatric illnesses yet is significantly heritable with and without BP patients

included in the pedigrees. This bipolarity index may be used to supplement BP diagnosis phenotype in future genetic studies.
Supported By: NIH
Keywords: Bipolar Disorder, Heritability, Bipolarity

F127. Polygenic Risk for Accelerated Molecular Brain Aging is Associated With Increased Depressive Symptoms and Blunted Corticolimbic Circuit Reactivity

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Background: Prior studies using postmortem human brain tissue have linked depression with gene expression patterns consistent with accelerated molecular aging of the brain. Here we identified common SNPs associated with this molecular phenotype and tested their cumulative impact on corticolimbic circuit reactivity in a sample of young adults.
Methods: Molecular brain age was determined based on gene expression in the orbitofrontal and ventrolateral prefrontal cortices in a large postmortem cohort (n=214, 44 women, age range: 16-91). A genome-wide association study was conducted to identify SNPs associated with the difference between chronological age and estimated molecular brain age. Top SNP hits were then used to create a polygenic risk score (PRS) for accelerated brain aging in the Duke Neurogenetics Study (n=1126, 633 women, mean age 19.72±1.25). This PRS was correlated with fMRI-assessed amygdala reactivity to faces, as well as self-reported symptoms of depression and anxiety.
Results: Three SNPs associated with accelerated aging survived the genome-wide $p<10\text{-}8$ significance threshold. Their combined PRS was associated with higher self-reported depression (b=0.071, p=0.016) and anxiety (b=0.066, p=0.029) symptoms across genders. The PRS was also correlated with reduced right amygdala reactivity to faces, relative to shapes, in men only (sex-by-PRS interaction: b=0.132, p=0.026; men: b=-0.110, p=0.012). This effect was primarily driven by amygdala response to neutral faces (interaction: b=0.157, p=0.008; men: b=-0.129, p=0.004).
Conclusions: Higher polygenic risk for accelerated brain aging may increase vulnerability to depression in young individuals. In men only, this effect may be accompanied by blunted amygdala reactivity to social salience.
Supported By: NARSAD Young Investigator Grant; Banting Postdoctoral Fellowship
Keywords: Brain Age, Depression, Genetics, Brain Imaging, fMRI

F128. Transcriptomics of Brain Age Gap Estimate (BrainAGE): Association Analysis of Depressed and Healthy Individuals

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Background: MRI imaging modalities, including T1-weighted (T1w) structural imaging, have been used with machine learning approaches to reliably predict the age of individuals. Brain Age Gap Estimate (BrainAGE), defined as the difference between a subject's predicted age and chronological age, captures deviation from typical brain aging. This study aims to discover association between variation in gene expression and age-dependent T1w-based brain morphometry variation (BrainAGE) using RNA-Seq gene-expression profiles from a study of major depressive disorder (MDD).
Methods: We trained the BrainAGE model on an independent data set of 420 healthy subjects using epsilon-Support Vector Regression (-SVR, radial kernel) with parameters tuned by 10-fold cross validation. For each of 157 study participants (78 MDD, 79 healthy), we predicted BrainAGE by taking the difference between the brain-estimated age and chronological age. We then performed a transcriptome-wide association of the BrainAGE phenotype with RNA-Seq gene expression data.
Results: For the MDD study, we found 12 gene associations with BrainAGE ($p<0.05$, adjusted). Notably, these associations include limitrin, a transmembrane-type immunoglobulin (Ig) superfamily protein that localizes specifically to the glia limitans, which are a component of the blood-brain barrier. We also found a significant association for astrocytic orosomucoid-2, which modulates microglial activation and neuroinflammation.
Conclusions: In our RNA-Seq study of MDD, genomic determinants of BrainAGE were involved in blood brain barrier regulation and neuroinflammation. The integration of age-dependent, MRI-derived morphological features with gene expression may provide insights into the gene regulatory mechanisms of depression.
Supported By: RO1
Keywords: BrainAGE, RNA-Seq, Major Depressive Disorder (MDD)

F129. Immunometabolic Depression: A Unique Biological and Genetic Profile

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Background: Major Depressive Disorder (MDD) is highly heterogeneous. Emerging evidence points towards a specific 'immunometabolic subtype' characterized by a unique biological profile. Evidence is provided for the following: 1) symptoms clustering within immunometabolic depression (i.e. hyperphagia) are specifically linked with alterations such as higher body mass index (BMI) and circulating levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha) and leptin; 2) these associations are rooted in shared genetic liabilities.
Methods: Phenotypic analyses were based on up to 1,062 patients (67.0% females) with current MDD from the

Netherlands Study of Depression and Anxiety (NESDA). Genetic analyses were based on 26,628 samples (59.1% females) from the Psychiatric Genomics Consortium (PGC), including 11,837 cases with lifetime MDD and 14,791 controls. GWAS data were used to build polygenic risk scores for BMI, CRP and leptin.

Results: A NESDA study on 808 MDD patients identified strong associations between the hyperphagia symptom and higher BMI (estimate=2.71, p<1.0e-4), CRP (estimate=0.33, p=4.0e-3). Similar analyses on 1,062 MDD patients showed that higher leptin was associated with hyperphagia (OR=2.34, p=1.9e-8), independently from BMI.

In analyses based on PGC, 15.8% of cases endorsed the increased appetite/weight symptom. These patients, as compared to controls, carried a higher polygenic risk for BMI (OR=1.18, p=1.6e-10), CRP (OR=1.08, p=7.3e-3) and leptin (OR=1.09, p=1.7e-3). These associations were not present for other MDD patients.

Conclusions: The constellation of biological alterations in immunometabolic depression may be rooted in a common genetic base and shared pathophysiological mechanisms. Full clinical and biological characterization of immunometabolic depression is warranted.

Keywords: Atypical Depression, GWAS, Immunoinflammation, Metabolic

F130. Association Study of Melatonin Pathway Genes With Seasonality and Circadian Preference in Bipolar Disorder

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Background: Bipolar disorder (BD) is a complex genetic disorder, therefore approaches using an endophenotype such as biological rhythm could be an alternative. In this study, we investigated the relationship between melatonin pathway genes and seasonal mood changes and circadian preference as life characteristics in bipolar patients.

Methods: Clinically stable BD patients (n = 324) were recruited from Samsung Medical Center and Seoul National University Bundang Hospital in South Korea. Circadian preference was measured using the standardized Korean version of Composite Scale of Morningness (CSM) and seasonality was measured with Seasonal Pattern Assessment Questionnaire (SPAQ). Genotype data was produced by using the Korea Biobank Array Chip (K-CHIP) v1.0. Four melatonin related genes (MTNR1a, MTNR1b, AANAT, ASMT) were selected and 34 SNPs was included for analysis after quality control.

Results: Seasonality was nominally associated with three SNPs in melatonin pathway gens, and after adjusting for multiple testing error rs116879618 in AANAT was remained significant (uncorrected P=0.0007). Circadian preference showed nominal associations with some SNPs but no SNPs were remained significant after multiple test correction.

Conclusions: 12 variants in AANAT, ASMT, MTNR1a and MTNR1b were nominally associated with seasonality and circadian preference of bipolar disorder. After correcting multiple test error, rs116879618 located in putative regulatory region of AANAT remained significantly associated with seasonality of bipolar disorder. This is first report that variant of melatonin pathway gene AANAT was related to seasonal mood and behavior changes of bipolar disorder. Further larger scale associative studies and biological mechanism studies are needed for clarify this association.

Supported By: National Research Foundation (NRF) of Korea grant (2015R1A2A2A01002699)

Keywords: Melatonin, Bipolar Disorder, Seasonality, Circadian Rhythms

F131. Genome-Wide Association Study Identifies Glutamate Ionotropic Receptor GRIA4 as a Risk Gene for Comorbid Nicotine Dependence and Major Depression

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Background: Smoking and major depression frequently co-occur. However, the genetic basis is poorly understood. This study aimed to detect genetic risk variants for comorbid nicotine dependence (ND) and major depression (MD).

Methods: We conducted GWAS in two samples of African-American participants (Yale-Penn 1 and 2), followed by meta-analysis. 3,724 nicotine-exposed subjects were analyzed: 2,596 from Yale-Penn-1 and 1,128 from Yale-Penn-2. Continuous measures (Fagerström Test for Nicotine Dependence (FTND) scores and DSM-IV MD criteria) rather than disorder status were used to maximize the power of the GWAS. Genotypes were ascertained using the Illumina arrays, followed by imputation.

Results: An intronic variant at the GRIA4 locus, rs68081839, was significantly associated with ND-MD comorbidity (beta coefficient = 0.69 [95% CI, 0.43-0.89], P = 1.53 × 10-8). GRIA4 encodes an AMPA-sensitive glutamate receptor that mediates fast excitatory synaptic transmission and neuroplasticity. Conditional analyses revealed that the association was explained jointly by both traits. Enrichment analysis showed that the top risk genes and genes co-expressed with GRIA4 are enriched in cell adhesion, calcium ion binding and synapses. They also have enriched expression in the brain and they have been implicated in the risk for other neuropsychiatric disorders.

Conclusions: GRIA4 is significantly associated with comorbid ND and MD. These effects appear to be mediated by variations in genes involved in neural signaling and the risk for other psychiatric disorders. Further research is needed to determine the replicability of these findings and to identify the biological mechanisms through which genetic risk for each condition is conveyed.
Supported By: RC2 DA028909, R01 DA12690, R01 DA12849, R01 DA18432, R01 AA11330, R01 AA017535, 2P50-AA012870, VA Connecticut Healthcare Center, Philadelphia VA MIRECCS and National Center for Post Traumatic Stress Disorder
Keywords: AMPA, Comorbidity, GRIA4, Major Depression, Nicotine Dependence

F132. The Effect of Telomere Length and Their Polygenic Risk Scores on Emotional Brain Function and Connectivity

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Background: Most literature to-date suggests that shortened telomere length (TL) amongst psychiatric disorder patients represents an effect of having the disease or the stresses precipitating it due to an increased release of stress hormones, immuno-inflammatory activation or oxidative stress. However, recent research indicates that a genetic predisposition to shortened TL might actually act as a risk factor for some types of mood disorders, and therefore shortened TL may play a causative role.TL has been associated with brain morphology, in the hippocampus, amygdala, posterior cingulate and precuneus. So far, no previous studies have considered the role TL may have on brain function during tasks relevant to mood disorders.
Methods: 112 participants underwent an fMRI session performing a facial-affect recognition paradigm. TL was quantified and polygenic risk scores for TL were constructed for all participants.
Results: First, TL was positively associated with increased activation in the amygdala, posterior cingulate/precuneus complex and cuneus during the facial-affect recognition task, and with increased effective connectivity from posterior regions of the face network to the ventrolateral prefrontal cortex (PFC). Secondly, the polygenic risk score for TL showed a positive association with medial PFC activation during facial affect.
Conclusions: To our knowledge, this study provides the first evidence linking TL and genetic risk for TL to brain activation and connectivity while categorizing emotional faces. The data support the view that TL and genetic load of TL influence the function of brain regions known to be involved in emotional processing and are part of the facial-affect processing network.
Supported By: NARSAD
Keywords: Telomere Length, Polygenic Risk Score, fMRI, Emotional Facial Processing, Brain Connectivity

F133. Genetic Variations Within Acyl-CoA Synthetase Bubblegum Family Member 1(ACSBG1) Gene Showed a Genome-Widely Significant Association With a Phenotype Dimension Characterized by Bulimic and Anxiety Comorbidities in Subjects With Bipolar Disorders

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Background: Given diverse disease course and symptom presentation, multiple phenotype dimensions with different biological underpinning are expected in bipolar disorders (BPs). Those dimensions are likely to be the intermediate phenotypes under the control of disease-susceptibility genes, or separate traits related to disease-modifier genes. This study aimed to identify genetic susceptibility loci associated with phenotype dimensions of BPs.
Methods: A total of 307 subjects with bipolar I (BP-I) and bipolar II (BP-II) disorders were included in the analysis. Symptom evaluations were performed on a lifetime basis. Through principal component factor analysis, six quantitative phenotypes representing lifetime clinical characteristics were identified. Genome-wide association analyses were performed for 833K single nucleotide polymorphisms (SNPs) using a linear association random effects model.
Results: Several genomic loci showed an association with phenotype dimensions with a genome-wide significance. Among them, the highest association signal was observed between two SNPs (rs17850484; p=1.32 * 10-10 and rs45444496; p=9.98 * 10-10) located on acyl-CoA synthetase bubblegum family member 1(ACSBG1) gene with a phenotype dimension characterized by lifetime comorbidities of bulimic and anxiety disorders. ACSBG1 gene encodes a protein possesses long-chain acyl-CoA synthetase activity, and the protein plays a central role in brain very long-chain fatty acids metabolism and myelinogenesis.
Conclusions: This study suggests the existence of genetic loci related to specific phenotype dimensions of BPs.
Supported By: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government(MSIP) (2015R1A2A2A01002699).
Keywords: Bipolar Disorder, GWAS, Symptom Dimensions, Anxiety Phenotypes, Bulimia Nervosa

F134. Intrinsic Neural Circuitry of Depression in Adolescence

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Background: Depressive disorders (DD) are a leading cause of disability worldwide, and their incidence increases sharply during adolescence, especially in females. Neurodevelopmental models attribute adolescent DD to abnormal neural responses in amygdala, striatum, and prefrontal cortex (PFC). However, affective and cognitive changes in DD are also implemented via rich interconnectivity of these regions which undergoes significant dynamic changes during adolescence. Here, we examined whether the strength of functional brain networks that include amygdala, striatum and PFC predict depression symptoms in adolescent females.
Methods: In this longitudinal study, we recorded resting-state functional connectivity (RSFC) using functional magnetic resonance imaging (fMRI) data in 174 adolescent females. We split data into training and testing subsets and examined two neural models using leave-one-out and 10-fold cross-validation approaches. Specifically, we related RSFC profiles within a network consisting of amygdala, striatum and PFC regions (within-circuit model) and connectivity of this network to the whole brain (extended-circuit model) to depression symptoms assessed concurrently and 18 months later.
Results: In testing subsets, the within-circuit RSFC profiles correlated with concurrent depression severity ($r = .29$, $p = .01$) and the extended-circuit model correlated with depression severity 18 months later ($r = .25$, $p = .01$). The connectivity within PFC, specifically anterior cingulate and ventromedial prefrontal cortex, contributed most to the correlation.
Conclusions: Our results demonstrate that RSFC based on functional brain networks involving amygdala, striatum and PFC are replicable neural signatures of concurrent and future depression symptoms in adolescent females. This represents a significant step towards identifying a neural signature of adolescent depression.
Supported By: RO1
Keywords: Adolescent Depression, Resting State fMRI, Ventromedial Prefrontal Cortex

F135. FKBP5 Methylation is Associated With Frontal-Limbic Brain Structure and Function in Depressed Adolescents and Healthy Controls

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Background: Individuals with depression display differences in frontal-limbic brain processes when compared to healthy controls. DNA methylation is an epigenetic process by which environmental factors regulate the expression of genes involved in depression. The current study examined the association between methylation of the FKBP5 gene (coding for FK506-binding protein 5, a key regulator in the negative feedback loop of glucocorticoids) and frontal-limbic brain structure and function in adolescents with depression and healthy controls.
Methods: 25 depressed adolescents (80% females) and 20 controls underwent a structural and functional brain imaging scan while judging the valence of a set of positive, negative and neutral pictures. DNA methylation of the FKBP5 intron-7 region was assessed from saliva samples. The relationship between FKBP5 methylation and brain volume and function in specific Regions of Interest was analyzed using multivariate regression.
Results: Greater FKBP5 intron-7 methylation was associated with reduced GM volume in the left ($p < .008$) and right ($p < .042$) hippocampus, regardless of diagnosis. Greater methylation was associated with greater amygdala activation in response to positive and neutral stimuli in controls, but not in depressed patients. Greater methylation was associated with greater activation in the lateral ($p < .033$) and anterior ($p < .037$) orbitofrontal cortex in depressed patients in response to positive stimuli, but not in controls.
Conclusions: These results suggest that the impact of glucocorticoids on brain structure and function may be differentially regulated by FKBP5 methylation in depressed individuals and controls. Further, they highlight the potential involvement of epigenetic mechanisms in frontal-limbic brain processes.
Supported By: RQSHA, CIHR
Keywords: DNA Methylation, Adolescent Depression, Neuroimaging

F136. Antidepressant Effects of Ketamine Versus Placebo are Differentially Associated With Brain Activity During Emotional Processing

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Background: Ketamine has shown rapid antidepressant effects in major depressive disorder (MDD). To learn about its mechanism of action, associations between its effects on symptomatology and brain function can be studied. We investigated the association between the decrease in depressive symptoms and the effects of ketamine versus placebo on fMRI activity during emotional processing.
Methods: 30 unmedicated patients with MDD participated in the double-blind placebo-controlled crossover study. After an infusion of ketamine (0.5 mg/kg) or placebo, participants were scanned at 3T fMRI during an emotional processing task. Depressive symptom severity was measured using the MADRS (Montgomery-Asberg Depression Rating Scale), and percent change was calculated from pre-infusion to scan day. Neuroimaging analysis was conducted with a linear mixed-effects model using factors of drug, MADRS percent change, and task components.
Results: We found an interaction between drug and percent change in MADRS (FWE-corrected $p<0.01$). In bilateral insula and cingulate, this interaction showed lower activation was

associated with a decrease in depressive symptoms post-ketamine, with the opposite trend found post-placebo. In bilateral parietal/occipital regions and middle/inferior frontal gyri, the interaction showed lower activation associated with decreased symptoms post-placebo, with no association found post-ketamine.
Conclusions: These findings showed that antidepressant effects were associated with ketamine versus placebo differentially in the brain. Decreased depressive symptoms were associated with lower activation in limbic/salience network regions post-ketamine, whereas this association was found in areas of central executive network post-placebo. Taken together, these results implicate distinct brain networks involved in the antidepressant response to ketamine as compared to placebo in MDD.
Supported By: NIMH Intramural Research Program Funding
Keywords: Ketamine, Brain Imaging, fMRI, Major Depressive Disorder (MDD), Emotional Processing, Placebo Effects

F137. Locus Coeruleus Signal Intensity is Decreased in Patients With Late-Life Depression Treated With Noradrenergic Agents

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Background: The Locus Coeruleus (LC), the major source of noradrenergic neurotransmission, can be visualized with neuromelanin-sensitive MRI. Although decreased signal intensity has been found in neurodegenerative and psychiatric disorders, it is not clear whether such alteration is similar across conditions and what confounding sources should be considered.
Methods: We assessed 37 patients with late-life major depression (MD) (mean age±SD=68.18±4.26), 21 patients with mild cognitive impairment (MCI) (mean age±SD=71.41±2.77), and 31 healthy controls (HC) (mean age±SD=67.00±4.06). All participants underwent a T1-weighted neuromelanin sensitive sequence. Left and right LC contrast ratios (LC-CR) were obtained by dividing LC T1 signal by the mean intensity of a cluster encompassing the medial aspect of midbrain and pons. Such LC-CRs were contrasted across the three groups, controlling for age and sex.
Results: MD patients showed decreased left and right LC-CR in comparison with the other two groups ($p=0.001$ and $p=0.003$), whereas there were no significant differences between MCI and HCs ($p=0.953$). Post-hoc analyses revealed that decreased LC-CRs were dependent on the use of noradrenergic medications (i.e., serotonin–norepinephrine reuptake inhibitors, SNRIs). MD patients under SNRIs ($n=25$) showed smaller LC-CRs than MD patients not using these medications ($p=0.017$), which did not differ from MCI and HC groups.
Conclusions: T1 signal intensity of noradrenergic LC neurons is specifically decreased in patients with late-life depression. Such effect is related with the use of SNRIs. Extracellular noradrenaline accumulation may deplete intracellular noradrenaline content, therefore decreasing neuromelanin-sensitive signal. Use of noradrenergic agents should be considered as a relevant confounder in analyses of LC integrity.
Supported By: Carlos III Health Institute (PIE14/00034; CP16/00048); FEDER funds, a way to build Europe.
Keywords: Late Life Depression, MCI, Locus Coeruleus, SNRI (Serotonin-Norepinephrin Reuptake Inhibitor), Structural MRI

F138. Effect of Ketamine Treatment on Amygdala Responsivity in Major Depressive Disorder

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Background: Major depressive disorder (MDD) affects a large portion of the world's population, yet standard treatments remain only partially successful. Ketamine, an NMDA receptor antagonist, is shown to induce rapidly acting antidepressant effects in patients with MDD. Since prior studies have shown amygdala hyperactivity for negatively valenced stimuli, in this study we sought to evaluate the effect of ketamine on amygdala responsivity after MDD patients received a series of 4 ketamine infusions.
Methods: Ten MDD patients received 4 infusions of intravenous ketamine (0.5 mg/kg), 2-3 days apart. At baseline (TP1), 24 hours (TP2) after the first and final (TP3) infusions, patients completed functional MRI while performing an affect labelling face-matching task. Functional images were processed using standard protocols and an amygdala region-of-interest was used to evaluate differences in mean activation for fearful faces versus objects across time points.
Results: Patients showed robust improvements in symptoms following ketamine ($p<.0001$). A significant overall effect for time was observed in the amygdala when contrasting responses to fearful faces and objects ($p<.04$). Specifically, hyperactivity to fearful faces decreased from TP1 to TP2 ($p=0.03$) and increased from TP2 to TP3 ($p=0.046$).
Conclusions: Ketamine treatment significantly reduced hyperactivity in the amygdala for fearful faces 24 hours following the first infusion. Mean activation returned to near baseline levels following the final infusion, perhaps suggesting habituation to the effects of ketamine. Future studies are needed to further understand the influence of ketamine on emotion and mood processing over longer time periods.
Supported By: U01
Keywords: Ketamine, Major Depressive Disorder (MDD), Task fMRI, Amygdala

F139. Functional Connectivity and Response to Ketamine Therapy in Treatment-Resistant Depression: A Pilot Study

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Background: Depression can be described as a brain-network disorder affecting functional connectivity. Ketamine is shown to induce fast-acting and robust antidepressant effects in patients with severe depression. The default mode network (DMN), a functional network involved in self-referential processing, is particularly implicated in depression. Here, we investigated whether intravenous ketamine leads to changes in DMN connectivity 24 hours following infusion in depression.
Methods: The Hamilton Depression Scale (HAMD) and resting-state fMRI was acquired from 15 patients experiencing a DSM-IV defined major depressive episode (35.412.1 years, 11 males) at baseline and 24 hours post-infusion (single sub-anesthetic dose of 0.5 mg/kg). To identify resting state networks (RSNs), ICA was run using FSL MELODIC and dual regression. Five RSNs associated with DMN were chosen to investigate changes in functional connectivity (FC) with anatomical ROIs selected a priori, including the anterior cingulate (ACC), posterior cingulate (PCC), hippocampus, and precuneus, as well as the amygdala.
Results: Depressive symptoms were significantly improved following ketamine treatment ($p<0.0001$). Decreases in FC between the DMN and the ACC, precuneus, right amygdala and right hippocampus were observed (all $p<0.05$, Bonferroni corrected).
Conclusions: Prior evidence suggests that depression pathophysiology may involve over-reactive ventral cortical-limbic brain networks, and reduced hyperconnectivity between the DMN and regions involved in depression have been reported for other antidepressant therapies. Our results show that a single infusion of ketamine similarly reduces FC within DMN networks. A normalization of DMN FC may thus contribute to the acute therapeutic effects of ketamine.
Supported By: U01
Keywords: Ketamine, Major Depressive Disorder (MDD), Resting State fMRI, Default Mode Network

F140. Neuroimaging Findings in Lithium Response Groups in Bipolar I Disorder: An Exploratory Magnetic Resonance Imaging Study

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Background: MRI studies in bipolar disorder (BD) have shown neurotrophic and neuroprotective effects of lithium, suggesting that this could be a pathway of its therapeutic effects. However, little is known about the neuroimaging differences among lithium response groups and its association with treatment efficacy. The objective of this study is to identify neuroanatomical and neurofunctional differences between lithium response groups and healthy subjects.
Methods: A cross-sectional exploratory study including 18 euthymic BD-I patients under lithium treatment and 9 healthy subjects matched by sex and age were included and evaluated using DIGS, HDRS, YMRS, GAF and Alda Scale. Based on the Alda Scale score, patients were divided in 2 groups, Lithium responders (Li-R n=7) and non responders (No-Li-R n=11). MRI was acquired in 3T scanner and a volumetric analysis was performed.
Results: There were no differences in demographic variables among the 3 groups. After adjusting by age, greater volumes were found in No-Li-R group when compared with controls in left thalamus ($p=0.007$), left hippocampus ($p=0.003$) and amygdala (L: $p=0.006$/R: $p=0.001$). Li-R group had greater volumes in left hippocampus ($p=0.007$) and right amygdala ($p=0.002$) compared with control group. There was no statistical significance when comparing Li-R vs No-Li-R groups.
Conclusions: Neuroanatomical differences were found in the patients' groups when compared with healthy controls in structures of the limbic system which has been widely implicated in the pathophysiology of BD. Possibly the mechanism underlying lithium response goes beyond its volumetric effects at the brain level. However, future studies with larger and prospective samples are required.
Supported By: Colciencias (PRISMA)
Keywords: Bipolar Disorder-I, Lithium, Magnetic Resonance Imaging, Psychopharmacological Treatment, Brain Imaging

F141. Cross-Network Associations With Rumination Across Late Adolescent Development

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Background: Objective: Rumination levels and depression are associated with disrupted connectivity within the default mode network (DMN) and between the DMN and cognitive control network (CCN). This study aims to test these associations of long-distance connectivity of these networks in both healthy and remitted-depressed adolescents and young adults (ages 12 – 28), during peak development.
Methods: One-hundred and five remitted (n=65) and healthy (n=40) participants, ranging from adolescence (n=38) to adulthood (n=67), completed a resting-state scan, diagnostic interview and a self-report on ruminative response style. Left and right posterior cingulate cortex (PCC; +/-5, 50, 36) seeds within the DMN were used to probe connectivity within-network and cross-networks (DMN-CCN). Significant clusters (Alpha Sim corr $p < .005$, $k > 57$) associated with rumination were identified within four regression analyses including

covariates to control for current depressive symptoms, age, sex, and motion translations, for a total family-wise error rate of $p < .04$.

Results: Across all participants, increasing rumination was associated with decreasing connectivity between left and right PCC with CCN regions including bilateral middle frontal gyrus, left inferior frontal gyrus, left inferior temporal gyrus and right precentral gyrus. No clusters within the DMN showed significant associations with rumination.

Conclusions: During the peak ages of depression onset and recurrence, rumination is associated with DMN cross-network connectivity with the CCN and is not associated with DMN within-network connectivity. Cross-network connectivity may be a regulatory response to reduce rumination, however, future work will need to directly test this hypothesis.

Supported By: R01MH091811 (SAL), R01MH101487 (SAL), UL1TR00050 (RHJ), Klingenstein Third Generation Foundation (RHJ), Varela Award from Mind and Life Institute (RHJ)

Keywords: Developmental Networks, Depression, Rumination, Cross-Network Connectivity

F142. Effect of Treatment Resistance Status on Whole Brain Voxel-Based Morphometry in Major Depressive Disorder

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Background: Treatment-resistant depression (TRD), defined as several failures to respond to treatment in patients with major depressive disorder (MDD), represents a large public health problem. Prior work has investigated regional brain differences between patients with MDD and non-depressed individuals, however few studies have investigated patterns in brain structure specific to TRD.

Methods: We examined the relationship between brain structure and treatment-resistance in a sample of unmedicated patients with MDD (N=61) and demographically similar healthy controls (N=41). All subjects underwent the Montgomery-Asberg Depression Rating Scale and an MRI for their brain at 3T. Patients were classified by treatment resistance according to the Maudsley Staging Model (MSM), which accounts for treatment trials, severity of illness and duration of presenting episode. Whole-brain voxel-based morphometry (VBM) analysis was conducted for both gray and white matter using Advanced Normalization Tools (ANTs). The model included age, sex, and MDD diagnosis as covariates, along with TRD (defined as >= 2 severity category in MSM).

Results: TRD patients had decreased white matter volume (1018mm3 cluster) in the splenium of the corpus callosum (x=18, y=-41, z=12) and gray matter volume (693mm3) in the right precuneus (x=15, y=-55, z=14) and retrosplenial cortex, compared to those without TRD.

Conclusions: TRD status was associated (over and above MDD status) with specific reductions in both white and grey matter volume in regions of particular importance to memory, as well as imagination and planning for the future. These data encourage additional research into brain-based abnormalities, as well as memory biases, specific to TRD.

Supported By: NIMH K23, NARSAD Young Investigator Award

Keywords: Depression, Brain Imaging, Treatment Resistant Depression, Voxel-Based Morphometry, Neuroimaging

F143. Commonalities and Distinctions in White Matter Integrity Associated With Suicide Behavior Between Adolescents and Young Adults With Bipolar Disorder and Major Depressive Disorder

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Background: Adolescence/young adulthood is a time when suicide behaviors often emerge. Adolescents/young adults with the bipolar disorder (BD) or major depressive disorder (MDD) are at especially high suicide risk. Brain circuitry abnormalities have been associated with suicide attempts (SAs) within each disorder, with increasing evidence in adolescents. However, it is not clear to what extent the brain circuitry of suicide risk is common to the disorders or whether there may be distinct circuitry differently associated with suicide risk within each disorder. We examined brain circuitry associating with suicide attempts across the disorders.

Methods: Eighty-one adolescents/young adults ages 14-25 years (85% female) underwent diffusion-weighted magnetic resonance imaging: 21 BD and 18 MDD with a history of SA, and 25 BD and 17 MDD without attempts (non-SA). Regional fractional anisotropy (FA) was compared between overall SA and non-SA groups and diagnosis/attempt subgroups ($p<0.005$, uncorrected).

Results: Left uncinate fasciculus FA was reduced in SAs vs. the non-SAs when assessing groups overall and within each diagnosis separately. Additional SA vs. non-SA differences included decreased FA in right uncinate and prefrontal anterior extension of left uncinate within BD, while increases in dorsal and posterior regions were observed within MDD.

Conclusions: Findings support common involvement in suicide behavior of the left uncinate fasciculus, a structure important in emotion regulation processes implicated in suicide, across BD and MDD. This implicates the left uncinate fasciculus as a target for suicide prevention across mood disorders. Circuitry features associated with SAs that differed between disorders suggest potential for differences in optimal targets.

Supported By: RC1; RO1; T32; NIDA; K25; American Foundation for Suicide Prevention; International Bipolar Disorder Foundation; Brain and Behavior Research Foundation; Women's Health Research at Yale; John and Hope Furth Endowment

Keywords: Bipolar Disorder, Major Depressive Disorder (MDD), White Matter Microstructure, Adolescents, Suicide Attempts

F144. Association of Cannabis Use With Brain Structure in Adolescents With Bipolar Disorder

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Background: Little is known regarding the association of cannabis use with brain structure in adolescents with bipolar disorder (BD). Therefore, we set out to examine this topic in a well-characterized sample of adolescents with BD and healthy control (HC) adolescents.
Methods: Participants included 114 adolescents (n=54 BD, n=60 HC), ages14-20 years; of these, 37 participants (n=29 BD, n=8 HC) reported lifetime use of cannabis. FreeSurfer-processed T1-weighted images, based on 3T MRI, yielded measures of cortical thickness, surface area (SA), and volume. Vertex-wise analyses complemented region of interest (ROI; amygdala, hippocampus, ventro-lateral prefrontal cortex (vlPFC), ventro-medial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC)) analyses. General linear models (GLM) covaried for age and sex. For volume and SA analyses only, intracranial volume was added as an additional covariate.
Results: ROI analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with greater reduction in vlPFC SA ($F=6.333$, $p=0.013$) in BD versus HC. Vertex wise analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with greater reduction in pars orbitalis ($F=12.055$, $p=0.001$) and rostral middle frontal ($F=10.457$, $p=0.002$) SA, middle temporal volume ($F=20.279$, $p<0.001$), and banks of superior temporal sulcus thickness (bankssts) ($F=17.397$, $p<0.001$) in BD versus HC.
Conclusions: These preliminary cross-sectional, retrospective findings suggest that the association between cannabis use and brain MRI phenotypes is moderated by BD diagnosis. Further studies are necessary to determine the direction of the observed association, and whether these associations also relate to neurocognitive dysfunction and/or symptom burden.
Supported By: Canadian Institutes of Health Research; Ontario Mental Health Foundation
Keywords: Bipolar Disorder, Cannabis, MRI Brain Imaging

F145. Differences in Emotional Attention Biases Between Suicide Attempters and Depressed Non-Attempters

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[1]National Institute of Mental Health

Background: Suicidal thoughts and behaviors are frequently associated with depression, which is also characterized by emotional processing deficits. Current research literature includes mixed findings about emotional attention biases in people with a history of suicide attempts compared to those without. Using an emotional dot-probe paradigm, this project seeks to examine emotional attention biases and their neural correlates in suicide attempters (SA) compared to depressed participants without an attempt history (NA).
Methods: 12 medication-free SAs ($M = 37.1$ y, 75% f) and 19 medication-free NAs ($M = 35.4$ y, 58% f) performed a dot-probe task in a 3T MRI scanner. The task used emotional (happy or angry) and neutral face stimuli on trials where the probe replaced either the emotional (congruent) or neutral (incongruent) face. Attention bias scores (incongruent − congruent reaction time) were analyzed using a linear mixed model in SPSS. fMRI data was analyzed using a multivariate model in AFNI.
Results: Behavioral analyses showed a significant emotion-by-group interaction. SAs displayed a greater bias toward happy faces compared to angry faces ($p<.05$), a difference which was not found with NAs. Neuroimaging analysis showed no significant group-by-emotion-by-congruency interaction, but there was a group-by-congruency-interaction found in the left precuneus (FWE-corrected $p<0.01$). We found lower activation during incongruent versus congruent trials in SAs, whereas there was no difference in NAs.
Conclusions: Results indicate that SAs are more biased toward happy face stimuli than angry compared to depressed NAs. These findings may suggest behavioral and neural endophenotypic differences between depressed suicide attempters and non-attempters.
Supported By: NIMH
Keywords: Suicide Attempts, Attentional Bias, Emotional Facial Processing, Depression, fMRI

F146. Reduced Orbitofrontal Cortex (OFC) Volume in Bipolar Adolescents With Suicide Attempts

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Background: Abnormalities in the orbitofrontal cortex (OFC) have been reported in adults with bipolar disorder (BD) with a history of suicide attempt. Few studies have examined the neural substrates of BD suicidal behavior, especially in youth. The aim of the present study was to investigate the relationship between suicide behavior and OFC volume in BD youth.
Methods: Thirty-six participants with BD, ages 13 to 21, completed a diagnostic interview, and mood rating scales. We examined lifetime symptoms of suicide ideation and behavior using the Columbia Suicide Severity Rating Scale. Participants underwent magnetic resonance imaging on a 3T Siemens Verio magnet. Morphometric analysis of brain images was

performed using FreeSurfer to evaluate differences in OFC volumes.

Results: Thirty-five participants had a history of suicidal ideation, and 18 participants had a history of suicide attempts. Between group analysis of variance revealed a significant difference in right OFC volume between suicide attempters and non-attempters. Specifically, BD youth with a history of suicide attempts had reduced right OFC volume, $F(1, 34) = 4.28$, $p < .05$. Additionally, Pearson's coefficient revealed a significant negative correlation between OFC volumes and suicide lethality, ($r = -0.58$), $p < .05$, demonstrating that as suicide lethality increased, OFC volume in BD youth was reduced.

Conclusions: The OFC plays a role in decision making, impulsivity, and reward circuitry which have shown to be impaired in BD. These findings suggest that suicide behavior in BD may be related to the emerging neuroanatomical substrates of the disorder, particularly abnormalities of the OFC.

Supported By: Depressive and Bipolar Disorder Alternative Treatment Foundation; Utah Science Technology and Research initiative

Keywords: Bipolar Disorder, Orbitofrontal Cortex, Suicide Attempts

F147. Resting State Oscillatory Power and Risk of Suicide in Depressed Patients

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[1]National Institute of Mental Health

Background: While recent EEG studies suggest an association between low frequency oscillatory power and suicidal ideation (SI), less is known about corresponding research in magnetoencephalography (MEG). We therefore sought to investigate the association between MEG oscillatory power changes in the theta, alpha, and beta bands and scores of SI.

Methods: Resting state MEG data were acquired in 1 or 2 sessions from 24 depressed subjects. Additionally, a factor score from an exploratory factor analysis using multiple behavioral measures, including items from the MADRS and the BDI, was calculated for each participant to reflect SI. A linear mixed effects model was used to calculate the relationship between power and scores of SI.

Results: There was a significant negative correlation between beta power and SI in regions including bilateral insula and dorsal cingulate ($pFDR<0.011$), and a positive correlation between theta power and SI in dorsolateral and dorsomedial prefrontal cortex ($pFDR<0.007$). We found no significant correlations between alpha power and SI ($p>0.05$). These results were not accounted for by changes in other depression ratings, indicating that the effects are specific to SI rather than depression alone.

Conclusions: These findings add to a growing literature which implicates the insula in depression. Our findings suggest that with increasing SI, there is a shift from higher to lower frequency oscillations during the resting state. It is notable that the bilateral insula and dorsal cingulate are part of the salience network, which is commonly activated in switching between the default mode network and the central executive network.

Supported By: National Institute of Mental Health

Keywords: Magnetoencephalography, Depression, Suicidal Ideation, Theta Band

F148. Emotion Processing Abnormalities in Bipolar Disorder: An fMRI Study Using an Emotional Go/Nogo Task

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Background: Bipolar disorder (BD) is characterized by emotion processing deficits; however, their neural underpinnings are still poorly understood. We previously identified an emotion processing bias, measured by an affective go/nogo (AGNG) task, as a potential neurocognitive endophenotype in BD. Stable BD and their siblings had a response bias toward negative emotional stimuli compared with healthy controls (HC). We aimed to expand our prior finding by examining the neural underpinnings of this negative emotional bias. Specifically, we aimed to compare fMRI activity in frontolimbic areas during an AGNG task in BD and HC.

Methods: Subjects: 10 euthymic BD patients and 15HC. Participants were scanned while performing an AGNG paradigm. They were asked to respond to or inhibit a response to happy, sad or neutral faces. fMRI data was analyzed using SPM. First-level individual analyses were conducted, applying the general linear model to assess the effects of inhibition and valence of the stimuli for each participant. In the second-level group analyses, voxel-wise statistical maps were used to examine effects across groups.

Results: BD patients had higher prefrontal activation ($p<0.05$) when inhibiting responses to happy (as opposed to sad) stimuli, compared to HC. Prefrontal cortex, cerebellum and limbic areas where less activated ($p<0.05$) in BD compared to HC during inhibition of negative distractors. Conversely, during inhibition of positive distractors BD patients showed higher prefrontal activation than HC.

Conclusions: Our preliminary, unpublished results are consistent with previous findings suggesting abnormalities in frontolimbic regions during tasks requiring inhibitory control of emotional stimuli in BD.

Supported By: NARSAD Young Investigator Award, Brain and Behavior Research Foundation grant and 1KL2TR001435 Faculty Scholar Award to MM Perez-Rodriguez.

Keywords: Functional Neuroimaging, Bipolar Disorder, Emotional Facial Processing, Social Cognition, Cognition Neuroscience

F149. Preliminary Evidence for Altered Synaptic Density and a Possible Role for Accelerated Ageing in Individuals With MDD as Measured With [11C]UCB-J PET

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Background: Converging evidence implicates synaptic and brain volume reductions in both major depressive disorder (MDD) and in aging. While measurement of synaptic density in humans previously relied on autopsy or biopsy, it is now possible to image synaptic density in vivo via quantification of synaptic vesicle glycoprotein 2A (SV2A) with the PET radioligand [11C]UCB-J. In a novel preliminary examination, we investigated MDD- and age-related synaptic density changes in vivo.
Methods: Ten unmedicated individuals with MDD (mean age=40.1±14.6) and ten age-, sex-, and smoking-matched healthy controls (HC; mean age=36.4±13.8) participated in a [11C]UCB-J PET scan. Volume of distribution (VT) was computed in prefrontal cortex (PFC), hippocampus, and globally using an arterial input function and a one-tissue compartment model.
Results: A MANCOVA with age as covariate across all ROIs revealed significantly lower synaptic density in MDD vs HCs ($F_{4,12}=3.999$, $p=0.027$). Synaptic density was significantly lower in dorsolateral PFC, orbitofrontal cortex, ventromedial PFC and hippocampus (all p's <0.02; all Cohen's $d>0.87$; 14% average difference). In the MDD group, greater severity of depressive symptoms was associated with lower global synaptic density ($r=-0.67$, $p=0.048$). Furthermore, we observed greater age-related reductions in global synaptic density in the MDD group only ($r=-0.75$, $p=0.019$; HCs $r=-0.26$, $p=0.501$).
Conclusions: These preliminary results suggest that MDD is associated with robust decreases in synaptic density and may accelerate synaptic density decreases associated with aging. Given that MDD is associated with increased risk for cognitive decline and Alzheimer's disease, recruitment is ongoing to determine whether MDD may accelerate the typical age-related synaptic density and cognitive changes.
Supported By: Nancy Taylor Foundation, VA NCPTSD
Keywords: Depression, PET Imaging, Aging, Synapses

F150. Neurofeedback of Frontal Response to Emotional Sentence in Healthy Subjects: A Functional Near-Infrared Spectroscopy Study

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Background: Frontal lobe dysregulation in major depressive disorder (MDD) to emotional stimuli has been reported. Improvement in emotional dysregulation using neurofeedback could be effective treatment for MDD. The aim of this study was to evaluate change of brain function during neurofeedback response to emotional stimulus in healthy volunteers.
Methods: Six-teen healthy volunteers were studied. This study was approved by the Institutional Review Board of Yamaguchi University Hospital. Relative change of oxygenated hemoglobin ([oxy-Hb]) in frontal area was measured by 52-channnel near-infrared spectroscopy (NIRS). The measurements were duplicated. The subjects listened to negative emotional sentence in four trials, did mindfulness breathing to change their brain activation in two trials, and did neurofeedback with mindfulness breathing from a display which showed [oxy-Hb] change in one trial. Through the experiment, subjects evaluated their mood by five grades (0; worst, 4; best) after each trial. We compared the [oxy-Hb] changes in each NIRS channel by using Paired-Student's t test with significance defined as false discovery rate (FDR) correction.
Results: The neurofeedback with mindfulness breathing showed a significant increase compared to the listening to negative emotional sentence in the centroid values (ch25-29, ch36-38, ch47,48) and the slope values (ch24-27, ch34-37, ch45, ch47), but not in the mean or integral values. The neurofeedback with mindfulness breathing significantly improved the mood of participants during the experiment.
Conclusions: Neurofeedback with mindfulness breathing could make the changes in frontal activation and improvement of mood.
Supported By: JSPS KAKENHI with grant numbers 25861011 and 16K10215
Keywords: Neurofeedback, A Functional Near-Infrared Spectroscopy, Depression, Emotion, Mindfulness

F151. GABAergic Neurotransmission Modulates Therapeutic Response to Ketamine Infusion in Major Depression

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Background: Animal models, and previous magnetic resonance spectroscopy (1HMRS) studies in humans suggest excitatory glutamatergic and inhibitory gamma-aminobutyric acid (GABA)-ergic neurotransmission contributes to the fast-acting antidepressant effects of treatments such as ECT. Here, we addressed whether changes in glutamate (Glu) and GABA levels associate with the rapid therapeutic effects of ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, in patients with major depression.
Methods: Using MEGA-PRESS 1HMRS with J-difference editing, we measured changes in Glu and GABA in the dorsal anterior cingulate cortex (dACC, voxel size: 20x30x40 mm3) prior to and 24-hours after 22 patients with major depression received a 40-minute infusion of intravenous ketamine (0.5 mg/kg). The Hamilton Depression Rating Scale (HAMD) assessed clinical response. Metabolites were analyzed with LCmodel software.

Results: Fourteen patients, defined as responders, showed >50% improvement in post-treatment HAMD scores. GABA, but not Glu, significantly increased 24-hours after ketamine treatment $F(1,20.99)=8.68$, $p=0.008$. A significant interaction showed that ketamine responders had lower levels of GABA relative to non-responders before commencing treatment $F(3, 24.86)=5.26$, $p=0.006$. Further, lower GABA levels prior to infusion predicted greater decreases in HAMD ratings within 24-hours of infusion $r(22)=0.57$, $p = 0.006$.

Conclusions: Results suggest ketamine leads to an upregulation of GABA, perhaps via glutamate to GABA synthesis, 24-hours post infusion, in line with at least one prior 1HMRS report of GABA increases during and immediately after ketamine administration. Findings further suggest that GABAergic transmission in the dACC prior to treatment modulates the extent of therapeutic response to ketamine in major depression.

Supported By: K24; UO1

Keywords: Depression, Ketamine, Magnetic Resonance Spectroscopy

F152. Determining Human Brain Modular Architecture Using Subject-Level Functional Multilayer Networks

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Background: Network disturbances have long been implicated in the pathophysiology of psychiatric disorders. However, to date, the identification of brain modular structure has been largely derived from group-level averaged networks, where individual variability in topological architecture and low-strength connections may be lost. Such subtle changes may be of particular relevance to psychopathology-related disturbances.

Methods: We used resting-state fMRI data from the Human Connectome Project, and a recent cortical multimodal parcellation [360 regions of interest (ROI)] supplemented by a subcortical-cerebellar parcellation [18+28 ROI]. While discrepancy resulting from first-level processing is often considered undesirable, we leveraged this variability to inform a robust determination of neural architecture. Multilayered network-ensembles were generated from the BOLD time-series using: 1) Pearson cross-correlation [weighted-signed], 2) Pearson cross-correlation post- global signal regression [τ=15% sparsity], 3) regularized inverse covariance [indexing partial correlations], and 4) mutual information [indexing nonlinear associations]. Using Louvain community detection and Rand index maximization, we identified 3 candidate resolution parameters [$\gamma1=0.9$; $\gamma2=1.6$; $\gamma3=2.3$]. The algorithm was run iteratively [i=500] for each subject-layer-resolution. An association-reclustering approach was used to achieve a stable, near-degenerate partition per γ.

Results: The following represents preliminary analyses on 10 subjects; full results will be included at the time of presentation. Each of the 3 resolution parameters yielded stable partitions (range=7-19 networks). Previously described (e.g., default-mode), and novel cortical-subcortical networks were identified.

Conclusions: The proposed coarse-fine network atlases can be adopted in future studies depending on the desired spatial scale. Pragmatic data-driven recommendations are made to future investigators based on dataset characteristics/use scenario.

Supported By: U.S. Department of Veterans Affairs National Center for PTSD; NIH (MH-101498); Brain and Behavior Foundation (NARSAD).

Keywords: Functional Neuroimaging, Brain Networks, Intrinsic Connectivity Networks, Modularity, Human Connectome Project

F153. The Effect of a 12-Week Aerobic Exercise Intervention on Neurometabolites in Young Healthy Adults Using 7T Magnetic Resonance Spectroscopy

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Background: Prolonged exercise has beneficial effects on cognition, which could be mediated by changes in neuronal metabolism. We present the first 7T magnetic resonance spectroscopy exercise study investigating neurometabolite concentrations before and after randomization to high-intensity (aerobic) exercise or low-intensity (toning) exercise in a large sample of healthy volunteers.

Methods: Fifty-two sedentary volunteers were randomized to 12 weeks of high or low intensity exercise. Subjects performed a maximal exercise test to obtain VO2max (reflecting cardiovascular fitness) and underwent magnetic resonance spectroscopy. Single-voxel spectra were collected from the left hippocampus and dorsal anterior cingulate cortex (dACC). Glutamate (Glu) and glutamine (Gln) concentrations were quantified using LCModel and repeated-measures ANOVA was used to test the interaction of exercise group and time. Pearson's correlation coefficient was used to assess the association between VO2max and neurometabolite changes.

Results: Forty-seven subjects completed the intervention. We found a main effect of time on VO2max ($F=4.58$; $p=0.04$), but the high-intensity group did not show a larger increase than the low-intensity group ($F=0.40$; $p=0.53$) (despite more time spent in the target heart-rate zone ($p<0.001$)). No significant interaction effect was found between time and group for any of the metabolites in the hippocampus nor the dACC ($p>0.05$). When combining both exercise groups, the change in VO2max correlated with Gln change in the hippocampus ($r=0.36$, $p=0.03$). In the dACC, when combining both exercise groups, the VO2max change showed a trend-significant association with Glu ($r=-0.29$, $p=0.07$).

Conclusions: Our findings suggest that exercise likely has widespread effects on neurometabolism, not restricted to hippocampus.

Supported By: Amsterdam Brain and Cognition
Keywords: Aerobic Exercise, Glutamate/GABA, MR Spectroscopy, Healthy Volunteers, Randomized Controlled Trial

F154. Impaired Interrelationships Between Thyroid and Adrenal Axes in Major Depression

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Background: Major depression has been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis as well as of the hypothalamic-pituitary-thyroid (HPT) axis. Evidence suggests that glucocorticoids inhibit thyrotropin (TSH) secretion via the glucorticoid receptors. However, in depression, their effects on the HPT axis are controversial.
Methods: To further investigate this issue, TSH response to 8 AM and 11 PM TRH tests, carried out the same day, and cortisol response to dexamethasone suppression test (DST) were evaluated in 218 drug-free DSM-IV major depressed inpatients and 50 healthy hospitalized controls.
Results: According to their DST responses, patients were classified into non-suppressors (n=56; 26% [DST+; i.e. highest post-DST cortisol level $>$ 120 nmol/L] and suppressors (n=162). Compared to controls, both DST suppressors and non-suppressors showed lower 11 PM-ΔTSH ($p<0.001$) and ΔΔTSH values (difference between 11 PM-ΔTSH and 8 AM-ΔTSH; $p<0.0001$). A robust correlation between 8 AM-ΔTSH and 11 PM-ΔTSH was found in controls ($r = 0.86$, $n= 50$, $p<0.0001$), in DST suppressors ($r = 0.85$, $n = 162$, $p<0.00001$) and in DST non-suppressors ($r = 0.81$, $n= 56$, $p<0.00001$). No significant differences were found between DST suppressors and non-suppressors for thyroid parameters.
Conclusions: Our data show that chronobiological HPT axis abnormality in depression (as reflected by reduced evening TSH response to TRH) is not secondary to HPA axis hyperactivity (as reflected by DST non-suppression). Taken together these results suggest that interrelationships between the HPA and HPT axes are affected during depressive states.
Keywords: HPA Axis, HPT Axis, Depression

F155. Blood Brain Barrier Integrity Biomarkers of Suicide in Adolescents

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Background: In adolescents, the risk of a second suicide attempt is approximately 30% after discharge from an inpatient psychiatric unit. Up to 78% of suicidal patients who subsequently died by suicide deny suicidal ideation in their last communication with a doctor. S100B an astroglilal protein has been described as a biomarker for blood brain barrier disruption.
Methods: Patients ages 12-18 were recruited after a suicide attempt or those who were admitted to the hospital for suicide risk. Healthy controls were matched by age, gender and BMI. Levels of several peripheral inflammatory (PIMs) biomarkers were drawn (S100B, IL1b, IL 6, IL-8, TNF alpha) as well as scales to measure the risk for suicide (C-SSRS). Samples were analyzed for PIMs. Suicidal patients ($N = 30$) and matched healthy controls ($N = 20$) have been recruited to date. PIMs levels were compared scores on the intensity, severity and ideation of the Columbia Suicide Severity Rating Scale (C-SSRS).
Results: Serum S100B levels were significantly higher ($p< 0.05$) in suicidal patients compared to healthy controls independent of psychiatric diagnosis. S100B correlated to suicidal ideation intensity ($P = 0.06$), ideation ($p = 0.05$) and severity ($p = 0.05$) as measured by the C-SSRS. Subjects with depression had increased IL-8 levels compared to healthy controls ($p <0.01$).
Conclusions: There is an urgent need for biomarkers to improve our ability to identify which youth are most likely to engage in suicide attempts. Increased S100B in adolescents with suicidal ideation suggests decreased integrity of BBB which could lead to a neuroinflammatory response.
Supported By: R21 NIMH MH108857
Keywords: Suicide, Neuroinflammation, Adolescents, Blood-Brain Barrier, Cytokines

F156. Anhedonia and Hopelessness/Dysphoria Associated With Tooth Loss in the Old Order Amish: Gender Differences and Neopterin Levels-Mediator or Confounder?

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Background: Tooth loss, marker of poor dental health, consequence of multiple causes including periodontal, endodontal, and traumatic etiologies, has been previously associated with mental illness. Proposed mediation of this link includes self-neglect secondary to depression and anhedonia. Yet, inflammation, a common consequence of poor dental health, has been previously predictively associated with depression (vicious cycle). As smoking and socioeconomically differences induce marked heterogeneity, we are now examining associations between tooth loss and symptoms of depression in the Old Order Amish (OOA) a more homogeneous adult population, largely nicotine free.

Methods: We studied tooth loss self-reports from 2831 Amish (57.3% women). Ratings of dysphoria/hopelessness and anhedonia, current and ever, were obtained from PHQ-9 and PHQ-2. Neopterin, a marker of cellular inflammation, was measured with ELISA. Logistic regressions with adjustment for age and gender, and secondarily, stratified by gender and adjusted for neopterin were used.
Results: Tooth loss was associated with current anhedonia but not hopelessness/dysphoria, past and ever either hopelessness/ dysphoria or anhedonia ($p<0.05$). When stratified by gender, in men only, tooth loss was associated with past either hopelessness/dysphoria or anhedonia. Adjustment for neopterin rendered all associations in the entire sample not significant, yet strengthen the associations in men, specifically for past either and ever either symptoms ($p=0.0062$ and 0.0098, respectively).
Conclusions: The associations of tooth loss with current anhedonia and both anhedonia and hopelessness/dysphoria seem mediated by inflammation, while the association with past symptoms in men is confounded by inflammation.
Supported By: P30 DK072488 NIDDK (NORC pilot/developmental grant PI T. Postolache) from the NIDDK, NIH, Bethesda, MD; the Joint Institute for Food Safety and Applied Nutrition, and the US FDA, through the cooperative agreement FDU.001418 (PI T.Postolache) and Intramural funds from University of Maryland School of Dentistry and Mood and Anxiety Program, Department of Psychiatry; MVM-CORE, Denver, CO.
Keywords: Tooth Loss, Depressive Symptoms, Anhedonia, Dysphoria / Hopelessness, Old Order Amish

F157. Infection and Increased Cortisol During Pregnancy and Risk for Adolescent Depression

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Background: Infection during pregnancy has been linked to increased risk of offspring depression and this relationship has been found to be moderated by maternal reports of prenatal stress. Despite findings that elevated cortisol also increases risk of infection, no studies have examined cortisol-immune interactions during pregnancy and risk for offspring depression.
Methods: Participants were derived from the Child Health and Development Study (CHDS), a prospective, longitudinal study of pregnant women and their offspring ($N=19,044$). The present study included participants from the Adolescent Study, a subsample of women from the original CHDS cohort whose offspring ($n=1,711$) were followed from birth to adolescence utilizing a series of assessments, including access to medical records, of which archived sera from 652 pregnant women were assayed.
Results: A multiple regression model was conducted to determine the effect of maternal infection and cortisol during the second trimester of pregnancy on measures of adolescent offspring depression. There was a significant interaction of second trimester infection and cortisol on adolescent depression scores, even after controlling for maternal education and infant sex, ($b = .404$, $SEb = .194$, $\beta = .275$, $p = .038$); Mothers who were diagnosed with an infection during the second trimester and experienced higher cortisol levels during this time had offspring with significantly higher depression scores than mothers of adolescents who were diagnosed with a second trimester infection alone.
Conclusions: Findings suggest that the association between infection during pregnancy and increased risk for offspring depressive symptoms depended on increased maternal cortisol.
Supported By: R01 MH096478
Keywords: Adolescent Depression, Cortisol, Pregnancy, Maternal Infection, Stress

F158. Toxoplasma Gondii-Oocyst Seropositivity and Depression in the Old Order Amish

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Background: Our group recently reported a positive association between Toxoplasma gondii (T.gondii) IgG serointensity

and current dysphoria/hopelessness in the Amish. There are two mechanisms by which humans can acquire foodborne toxoplasmosis; i.e. via ingestion of oocysts or tissue cysts. T.gondii oocysts, which are present in cat feces and contaminated soil, water and vegetables, are highly resilient to common methods of disinfection, are more virulent than tissue cysts, and may have higher neurotropism, with a possible higher potential to induce behavioral and affective dysregulation. With the novel availability of methods to detect oocyst-specific antibodies, we now investigated for the first time ever, the relationships of dysphoria/hopelessness and anhedonia with T.gondii-oocyst seropositivity.

Methods: In 777 Old Order Amish with mean (SD) age of 42.4 (17.0) years, including 61.4% female participants from two studies- Amish Wellness Study and Thrifty Microbiome, depression screening questionnaires (current and life-long PHQ 2), T. gondii IgG anti-oocyst antibodies, and whole T.gondii IgG antibodies were assessed using ELISA. With adjustment for age and sex, logistic regression models were used to analyze current and life-long symptoms of dysphoria/hopelessness, anhedonia, and a combination of both these symptoms, in relationship to T.gondii-oocyst seropositivity.

Results: T.gondii-oocyst seropositivity was positively associated with current combined dysphoria/hopelessness and anhedonia ($p=0.038$). No statistically significant relationships were identified between life-long dysphoria/hopelessness, anhedonia, or current symptoms in isolation, and T.gondii-oocyst seropositivity.

Conclusions: Confirmation in longitudinal studies of seroconversion and reactivation may lead to specific targeting of oocyst-transmitted T.gondii infection, in particular in individuals with refractory depression and/or high suicide risk.

Supported By: Distinguished Investigator Award from the American Foundation for Suicide Prevention (DIG 1-162-12, T.Postolache); P30 DK072488 NIDDK (NORC pilot/developmental grant PI T. Postolache) from the NIDDK, NIH, Bethesda, MD; the Joint Institute for Food Safety and Applied Nutrition, and the US FDA, through the cooperative agreement FDU.001418 (subproject PI T.Postolache); and the MHBA-016-15S, Merit Award from VA CSR&D (T Postolache and L.Brenner).

Keywords: Toxoplasma Gondii, Oocyst IgG, Anhedonia, Old Order Amish, Hopelessness

F159. Cell -Specific Ablation of RAGE Alters Susceptibility to Depressive-Like Behaviors After Chronic Unpredictable Stress

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Background: Growing evidence suggests that innate immune cells such as microglia, promote neuroinflammation in response to stress by releasing danger associated molecular pattern (DAMP) molecules leading to increased inflammatory signaling through their ligation to pattern recognition receptors such as toll-like receptor 4 (TLR4) and the receptor for advanced glycation end-products (RAGE). Our preliminary studies show that microglial RAGE is upregulated in response to chronic unpredictable stress (CUS) and enhanced microglial RAGE expression coincides with the onset and recurrence of stress-induced depressive-like behaviors. Most importantly, constitutive RAGE KO mice show an attenuation of stress-induced behavioral effects. These novel findings suggest that stress-induced depressive like behaviors may be partial mediated through enhanced microglial DAMP-RAGE signaling.

Methods: We generated RAGEfl/fl:CAMKIIaCre and RAGEfl/fl:CX3CR1CreERT mice and utilized tamoxifen-induced Cre recombinase system for cell-specific knockout of neuronal or microglial RAGE, respectively. Neuronal and microglial RAGE knockout (KO) mice were tested for cognitive, anxiety and depressive-like behaviors after CUS exposure using novel object recognition (NOR), forced swim test (FST) and sucrose consumption test (SCT).

Results: Microglial RAGE deletion blunted stress-induced microglial reactivity following CUS and promoted resilience to stress-induced anhedonia as assessed by the sucrose consumption test. However, microglial RAGE deletion had no effect in the FST or NOR tests. Interestingly, neuronal RAGE deletion failed to protect knockout mice against stress-induced anhedonia but promoted resilience to both despair (FST) and cognitive impairment (NOR) following CUS exposure.

Conclusions: Together, these data provide novel insights into the role of RAGE signaling in stress-induced microglial reactivity and the development of depressive-like behaviors.

Supported By: Mears endowment to Ronald Duman; State of Connecticut

Keywords: Microglia, DAMPs, Chronic Stress, Depression, Cognition

F160. Cortisol Response to Acute Stress is Associated With Differential Abundance of Taxa in Human Gut Microbiome

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Background: Altered gut microbiota are observed in stress-related disorders such as depression, but associations between acute stress response and gut microbiota are unknown. We assessed whether cytokine and cortisol response to an acute psychosocial stressor were associated with gut microbiome composition in psychiatrically healthy pregnant women.

Methods: Women were recruited from a study examining stress and pregnancy. Stool was sampled at 20-26 weeks gestation. At 21-34 weeks gestation, participants underwent a twenty-minute laboratory stressor (Trier Social Stress Test; TSST); serum cytokines (interleukin(IL)-6, tumor necrosis factor-α (TNFα), interferon-γ (IFNγ)) and cortisol were collected pre and post-stressor (T-5, T+30, T+65, T+140); area under the

curve (AUC) represented response over time. 16S sequencing was performed, purified products were analyzed using Illumina MiSeq. Alpha diversity was measured in operational taxonomic (OTUs) at 10,000 read depth, and Shannon index. Beta diversity was measured with un/weighted UniFrac distances. Differential abundance was assessed in taxa with >1% mean abundance across samples; multiple tests were corrected via Benjamini-Hochberg method; false discovery rate (fdr)<0.05 were significant. Permutation Multivariate Analysis of Variance tested associations of microbiome composition with cytokines and cortisol.

Results: n = 17 women completed the TSST. There was a significant association between cortisol AUC and unweighted UniFrac distance (p=0.041). Cortisol AUC was positively associated with differential abundance of Ruminococcaceae (fdr<0.0001), Prevotella (fdr<0.0001), Ruminococcus (fdr=0.04), and negatively with Bacteroides (fdr=0.006), Megasphaera (fdr=0.0001), and Eubacterium (fdr=0.028).

Conclusions: Cortisol response to acute stress was associated with differential abundance of several gut taxa; further exploration of links between hypothalamic-pituitary-adrenal axis and gut microbiome is needed.

Supported By: March of Dimes, NIMH K23, NARSAD Young Investigator

Keywords: Gut Microbiome, Cortisol, Trier Social Stress Test, Inflammatory Cytokines, Hypothalamic Pituitary Adrenal (HPA) Axis

F161. Proteomic Analysis of Blood Based Samples From the OPTiMiSE (OPtimization of Treatment and Management of Schizophrenia in Europe) Study Point Towards Complement Pathway Protein Changes

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Background: The OPTiMiSE trial may help in identification of predictors of treatment response. Medication naïve patients with first episode schizophrenia or schizophreniform disorder were enrolled in the study and treated for a four-week-period with amisulpride. 30 non-remitters (as defined by the Andreasen criteria) and 30 remitters were selected to represent good and poor outcome groups.

Methods: We compared proteomic markers in serum collected prior to treatment in 30 patients who showed a good response to amisulpride ("responders"), and 30 patients who did not show a good response ("non-responders"). Serum samples were depleted using HPLC. 50 μg from each sample were run for a 90 min gradient on a Quadrupole-Orbitrap Mass Spectrometer. Raw MS data were processed and searched against the human Uniprot database, for quantitation of peptides and proteins. False discovery rates (FDR) were set at 1% for both peptide and protein levels.

Results: 464 protein identifications were obtained. Samples were excluded where >30% of proteins were missing, and this left 228 proteins for analysis. Of these, 21 were significantly different between responders and non-responders. Pathway analysis of the significant proteins determined "complement and coagulation cascades" to be the top pathway affected with six proteins from the list assigned to the pathway. These were CFI, C4A, C6, F9, VWF and SERPING1, all found up-regulated.

Conclusions: Our data identifies the complement proteins in treatment response and this is consistent with our previous findings of up-regulation of the complement pathway among those at risk of psychotic experiences.

Keywords: Proteomics, Schizophrenia, Complement Proteins

F162. NLRP3 Polymorphism and Peripheral Levels of Interleukin-1β in Patients With Major Depressive Disorder

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Background: Recently, increased expression of NLRP3 complex proteins was found in peripheral mononuclear cells of patients with major depression disorder (MDD) (Alcocer-Gomez et al., 2017). This cross-sectional population-based study explored the effect of a single nucleotide polymorphism rs10754558 (C/G) in the NLRP3 gene, serum levels of IL-1β and MDD.

Methods: Our study included 1,110 subjects (18 – 35 years old). MDD diagnosis was performed using the structured diagnosis interview, MINI 5.0. DNA was extracted from peripheral leucocytes and the SNP (rs10754558, C/G) was genotyped by qPCR. Serum samples were used for determination of IL-1β levels. Statistical analysis was performed using χ2-test, two-way ANOVA followed by Bonferroni post-hoc test, and logistic regression, as appropriate.

Results: This study comprised 615 (55.9%) controls and 485 (44.1%) subjects with MDD. No differences were found in the prevalence of MDD according to genotype, even after adjusted analysis. In a subsample of 161 individuals we observed that the GG genotype was associated with higher IL-1β levels when compared to CC or CG genotypes. In addition, higher levels of IL-1β were found in MDD subjects with the GG genotype compared to subjects with CC or CG genotypes.

Conclusions: These results suggest that the G allele of the SNP rs10754558 in NLRP3 gene, which was described as a gain of function, was not associated with MDD per se, but it was associated with higher levels of IL-1β in patients with MDD. Thus, in patients with the GG genotype the MDD diagnosis is more likely associated with inflammatory dysfunction.

Supported By: International Society for Neurochemistry (ISN), Brazilian National Council for Scientific and Technological Development (CNPq)
Keywords: Depression, Inflammation, NLRP3 Inflammasome, Polymorphism, Inflammatory Cytokines

F163. Inflammation is Associated With Mesolimbic Reward Circuitry in Major Depression

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Background: Growing evidence implicates immune dysregulation in major depressive disorder (MDD), which impacts mood state via changes in a central 'reward circuit' that includes dopaminergic projections from the ventral tegmental area to nucleus accumbens (VTA−NAc).
Methods: We measured peripheral pro-inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) in 17 MDD subjects (6 female, age=39.5 ±11) and 15 HV (5 female age=36.2 ±10). High-resolution resting-state functional magnetic resonance imaging (fMRI) was collected using a multi-echo multi-band acquisition sequence for improved temporal resolution and signal power, particularly for subcortical structures. Functional connectivity between bilateral VTA−NAc was computed and correlated with the pro-inflammatory markers, controlling for age and gender.
Results: The MDD group reported higher depressive symptoms (MADRS: MDD=28.2 ±4; HV=0.8 ±1; $p<0.001$) and anhedonia (SHAPS: MDD=35.8 ±7; HV=17.4 ±4, $p<0.001$). There were no significant group differences in CRP (log CRP: MDD=0.17 ±0.6; HV=0±0.3) or IL-6 (log IL-6: MDD=29.2 ±35; HV=24.4±21). However, in the MDD group, both IL-6 and CRP were positively correlated with VTA−NAc connectivity (IL-6, R=0.7, p=0.024; CRP, R=0.5, p=0.045), which remained significant when controlling for depressive symptoms, anhedonia and each other. Interestingly, VTA−NAc connectivity was positively correlated with anhedonia in the MDD group (R=0.5, p=0.049), which became insignificant when controlling for IL-6 and CRP, suggesting the relationship between mesolimbic connectivity and anhedonia might be mediated by inflammation.
Conclusions: These findings suggest a link between peripheral inflammatory markers and the integrity of the central reward circuit, which might mediate anhedonia.
Supported By: R21MH109771
Keywords: Inflammation, Neuroimaging, Depression, Anhedonia, Reward

F164. Epidermal Growth Factor and Fibroblast Growth Factor-2 Circulating Levels in Elderly With Major Depressive Disorder

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Background: Previous studies indicated that major depressive disorder (MDD) may occur as a result of the changes in neuronal plasticity. Epidermal growth factor (EGF) is a well-known factor involved in neuronal growth and synaptic plasticity. Fibroblast Growth Factor-2 (FGF2) is important for neocortical development, survival and growth. In this study, we aim to investigate the serum levels of EGF and FGF2 in elderly with MDD as no particular studies of EGF and FGF2 have been conducted in this population.
Methods: Study population comprised of 99 patients diagnosed with MDD based on DSM- IV (age: 71.16±7.95) and 51 healthy control group (age: 72.34± 8.02). The EGF and FGF2 were studied by using LUMINEX platform
Results: There were also no significant differences between the patient groups and healthy controls in terms of serum levels of EGF (p= 0.383) and FGF2 (p = 0.428). Female patients were found to have higher levels of EGF than male patients (p=0.004). HDRS score is correlated to serum levels of FGF2 in the patient group (p= 0.009, r=0.297).
Conclusions: The present study demonstrated no significant differences of serum EGF and FGF2 levels between the patient group and the control group. We did not find any significant correlation between the serum EGF and FGF2 levels but EGF is affected by gender and HDRS score is correlated to serum levels of FGF2 in the patient group. Further studies with larger samples are needed to determine whether EGF and FGF-2 might be useful pathophysiological indicators of depression especially in elderly.
Keywords: MDD, VEGF, FGF2-AS, Elderly, Cognitive Performance

F165. Resting Motor Threshold in Adolescents With Major Depressive Disorder

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Background: Transcranial magnetic stimulation (TMS) is emerging as both a probe of function and as an intervention in major depressive disorder (MDD) in youth. Resting motor threshold (RMT) serves as the basis for the individualized 'dosage' of TMS. To date, it is not known if it differs between diagnostic groups in youth.
Methods: Forty-one adolescents between the ages of 12 to 18 years participated. Sixteen were healthy controls (9 males, 7 females) and twenty-five were adolescents with MDD (13 males, 12 females). RMT was defined as the minimal stimulator intensity required to evoke a motor response greater than 50μV in the subject's right FDI muscle (hand) in 5 out of 10 trials when stimulating the contralateral motor cortex (M1). We compared the two group, the effect biological sex within groups, and correlation with age. To control for multiple comparisons $p < 0.02$.
Results: RMT was 23% higher in adolescents with MDD compared to healthy controls ($t = -3.36$, $p = 0.002$).

RMT was significantly higher in females when compared to males in the control (t = -2.55, p = 0.02, 27% higher in females) group and demonstrated a trend in the MDD group (t = -2.21, p = 0.037, 15% higher in females). Age was not correlated with RMT in either group.

Conclusions: As the application of TMS both as a probe of function and an intervention in pediatric samples grows, considerations on the variability of RMT across diagnostic groups and biological sex merit further investigation.

Keywords: Repetitive Transcranial Magnetic Stimulation, Motor Threshold, Developing Brain, Adolescent Depression, Brain Stimulation

F166. Imaging Biomarkers of Subcallosal Cingulate Deep Brain Stimulation for Treatment Resistant Depression

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Background: Subcallosal cingulate (SCC) is one potential target for deep brain stimulation (DBS) therapy in treatment resistant depression (TRD). Average response rates to SCC-DBS in TRD are 50% at 6-12 months in open-label studies. However, it remains unknown which 50% respond. There is currently no evidence-based approach for patient selection. Brain imaging biomarkers could provide clinically useful predictors of efficacy.

Methods: Brain glucose metabolism was measured with FDG-PET at baseline and 6 months post-DBS in 20 patients with TRD who participated in a SCC-DBS trial. Retrospective comparisons of baseline metabolic activity were performed between responders (N=11) and non-responders (N=9). Responders were defined as $\geq$ 50% reduction after 6 months of DBS in 17-item Hamilton Depression Rating Scale (HDRS) from baseline scores.

Results: Region of interest analysis showed that SCC and caudate metabolism were significantly higher in responders compared to non-responders after controlling for age. There were positive correlations between SCC metabolism at baseline and HDRS change at 6-months (r=0.541; p=0.017), whereas the correlation between caudate metabolism and change score only appeared at a trend level (r=0.444; p=0.057). Whole brain multiple regression showed a positive relationship between baseline SCC activity and 6-months change scores ($p<0.001$ uncorrected). Responders had a significant decrease in metabolic activity in SCC (p=0.003) and caudate (p=0.030) at 6 months post-DBS, whereas responders showed no change in SCC and caudate.

Conclusions: The identification of baseline SCC and caudate metabolic activity as a predictive marker of SCC-DBS outcome needs further prospective study, but suggests that FDG-PET should be performed in patients undergoing SCC-DBS.

Supported By: CIHR CRIO Project grant

Keywords: 18FDG PET, Deep Brain Stimulation, Depression, Subcallosal Cingulate

F167. Remotely Programmed Deep Brain Stimulation of the Bilateral Habenula for Treatment-Resistant Major Depression: An Open-Label Pilot Trial

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Background: The habenula (Hb) is an epithalamic structure located at the center of the dorsal diencephalic conduction system. Hyperactivity of the lateral habenula (LHb) is thought to drive depression-related midbrain activity. Deep brain stimulation (DBS) of the major afferent bundle (i.e., stria medullaris thalami) of the LHb can treat treatment-resistant major depression (TRD). However, direct habenular stimulation is difficult to achieve due to its structural invisibility.

Methods: We use quantitative susceptibility mapping (QSM)/T1-w hybrid image generation to view Hb, and investigate the effectiveness of bilateral Hb DBS for patients with TRD. Conventional T1-weighted MR imaging and quantitative susceptibility mapping are incorporated to generate a hybrid contrast to guide registration for atlas construction. The resulting QSM/T1-w hybrid images preserve both the enhanced anatomical contrast of deep brain nuclei in the susceptibility map and clear cortical structures defined in the T1-weighted image. Furthermore, we use a novel DBS system with remote and wireless programming capabilities. (ClinicalTrials.gov, Identifier: NCT03254017)

Results: Two patients treated with DBS for at least three months were evaluated. Patient 1 exhibited no changes in anhedonia or depressive symptoms; patient 2 showed alleviation of depressive symptoms. Although there were no adverse events of remote programming, patient 2 reported numbness of the left pinky finger and coldness of the mouth after stimulation.

Conclusions: This research primarily demonstrates that (QSM)/T1-w hybrid image generation can reveal Hb, and that its stimulation may benefit some patients with TRD. Furthermore, remote programming of DBS can markedly enhance patient convenience and minimize total treatment time, with no remote-specific disadvantages.

Supported By: National Natural Science Foundation of China Grant (81771482), Shanghai JiaoTong University School of Medicine-Institution of Neuroscience (SHSMU-ION) Research Center for Brain Disorders (to B.M.S.)

Keywords: Neuromodulation, Deep Brain Stimulation, Treatment Resistant Depression, Lateral Habenula

F168. Relationship Style in Major Depression and Bipolar Types I and II

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Background: Relationship style can influence the patient-physician relationship, adherence to treatment recommendations and course of illness. Insecure attachment styles are more prevalent in individuals with mood disorders and has been associated with worse clinical outcomes, whereas a secure attachment is linked to more positive health behaviors, such as greater adherence to health plans and preventive health behaviors. Aim: To examine the prevalence of close relationship/attachment styles in patients with major depression (MDD), bipolar type I (BPI) or bipolar type II (BPII).
Methods: 219 participants were recruited from the Mood Disorders Program of the McGill University Health Center in Montreal, Quebec. Mood diagnoses were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Relationship/attachment styles were assessed using the Experiences in Close Relationships Questionnaire, anxious and avoidant attachment styles were examined. One-way ANOVA and Tukey post-hoc tests were conducted to examine the prevalence of attachment styles within each diagnostic group.
Results: The prevalence of anxious attachment differed in the MDD, BPI and BPII groups ($F(2, 180) = 5.652$, $p = .004$). There was no difference in prevalence of avoidant attachment style between the groups. Post-testing revealed that the BPII (4.5 ± 1.31) scored significantly higher than the BPI group (3.73 ± 1.25, $p = .003$).
Conclusions: Bipolar type I and type II groups may develop different type of relationships with their treatment team as a consequence of their attachment patterns. Modification of treatment approaches may be warranted.
Keywords: Bipolar Disorders, Attachment, Mood Disorders

F169. Using Speech Characteristics for Assessment of PTSD or TBI in a Military Population

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Background: The aim of this study is to demonstrate that speech characteristics, derived from audio recordings of a subject, can be used to assess the subject's mental health state, i.e. PTSD, TBI or healthy.
Methods: We used recordings from 202 subjects: 50 with PTSD, 60 with TBI and 82 controls and analyzed PTSD vs control and TBI vs control separately. A variety of speech features were extracted from the recordings, such as articulatory features, prosodic, spectral, temporal, speaker characteristics etc., including short (frame level), segment level and session level statistics, and were used to train and evaluate a classification model for each target category (PTSD and TBI). We performed N-fold cross validation experiments to assess the performance of our classifiers. For each fold the majority class was down sampled in order to achieve equal priors for each class, and then the data was split into three equal and balanced splits: feature section and training was performed on two thirds of the data and one third was used for validation. We used random forest (RF) classifiers for prediction and explored different techniques for feature selection.
Results: The most successful feature selection approach used the two sample Wilcoxon rank sum test, and a strict P value threshold. The results were averaged across 150 (50-folds x 3 splits) different validation sets and demonstrated an AUC around 0.75 for PTSD and AUC around 0.7 for TBI.
Conclusions: These results demonstrate the speech-based measurements can provide important information towards automated assessment of a subject's mental health.
Supported By: Cohen Veterans Bioscience, Telemedicine and Advanced Technology Research Center
Keywords: PTSD - Posttraumatic Stress Disorder, TBI, Speech Markers

F170. Monoamine Oxidase Inhibitor Use in an Adult Patient With Treatment Resistant Depression

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Background: This poster will describe the clinical course of a patient with treatment refractory depression who developed significant hypotension during treatment with Tranylcypromine and was subsequently treated with Phenelzine.
Methods: This is a case report that describes the treatment of a patient with treatment refractory depression who developed clinically significant side effects in response to one MAOi, who was later successfully managed with an alternative MAOi.
Results: The patient exhibited a clinical benefit to Phenelzine, with no significant changes to her blood pressure.
Conclusions: Patients that experience significant side effects from one MAOi may be successfully managed on another MAOi without developing similar side effects.
Keywords: Antidepressants, Major Depressive Disorder (MDD), Adverse Effects

F171. Ketamine Modulates Kynurenine Pathway in Mood Disorders: A Longitudinal Structural Equation Model

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Background: Growing evidence from both animal and human clinical studies supports the hypothesis that the underlying pathophysiology of depression implicates dysfunction in wide array of systems, including immune, monoaminergic and glutamatergic system. One potential intersection point for these three systems is the kynurenine(KYN) pathway of tryptophan metabolism. Using structural equation modelling (SEM), we explored the potential impact of ketamine on attenuating the

pro-inflammatory effects of KYN pathway activation in subjects with bipolar disorders (BD).

Methods: Thirty-nine BD patients with treatment-resistant depression (23F, 18-65-years-old). Subjects received a single infusion of ketamine (0.5 mg/kg) over 40 minutes. Using specific ELISA kits, KYN pathway analytes—including plasma concentration of indoleamine-2,3-dioxygenase(IDO), kynurenine, kynurenic acid(KA), and quinolinic acid(QA)—were studied at 60 minutes prior to infusion (baseline), and 230 minutes, Day 1, and Day 3 post-infusion. We used a multivariate panel model that includes contemporaneous crossed effects between the metabolites.

Results: IDO levels were significantly reduced at all three time points. Inversely, ketamine administration significantly increased both KYN and KA levels at Day 1 and Day 3. No change in QA levels was observed post-ketamine. Interestingly, a post-ketamine reduction in the QA/KYN ratio was observed at Day 1. We observed that at baseline pro-inflammatory cytokines and behavioral measures predicted change in the KYN pathway in response to ketamine.

Conclusions: Results suggest that SEM is useful in explaining highly complex interrelated pathways that targets immune, monoaminergic and glutamatergic system. In addition, single ketamine treatment appears to significantly modulate the confluent path providing further evidence of its potential therapeutic properties in mood disorders.

Supported By: The Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH) (NCT00088699 and 04-M-0222) by a NARSAD Independent Investigator and by the Brain & Behavior Mood Disorders Research Award to Carlos A. Zarate Jr, MD.

Keywords: Structural Equation Modeling, Kynurenine Pathway, Quinolinic Acid, Ketamine, Treatment Resistant Depression, Mood Disorders

F172. Clinical Evaluation of Abuse Potential of ALKS 5461

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Background: ALKS 5461 is an investigational opioid system modulator for adjunctive treatment of major depressive disorder (MDD) comprised of buprenorphine (BUP) and samidorphan (SAM), a μ-opioid receptor antagonist added to address the abuse/dependence potential of BUP. The ability of SAM to address the abuse potential of BUP in the ALKS 5461 combination was explored.

Methods: Study 212 evaluated abuse potential in nondependent, opioid-experienced volunteers. Participants were randomized to 6 treatments in a blinded crossover design: Placebo (PBO), ALKS 5461 at the therapeutic dose (BUP/SAM 2mg/2mg), and at 4X (8mg/8mg) and 8X (16mg/16mg) supratherapeutic doses, and BUP (8mg and 16mg). Separately, safety data from 4 PBO-controlled MDD studies (N=961) were interrogated for adverse events (AEs) that may be associated with euphoria, dependence and withdrawal.

Results: In Study 212 (n=38), maximum effect (Emax) Drug Liking scores for the ALKS 5461 2mg/2mg dose were similar to those for PBO (median within-subject difference [90% CI]: 2.5 [0.0-9.0]). Emax Drug Liking scores for the ALKS 5461 dose groups, including supratherapeutic doses, were significantly lower than those observed for either BUP dose. In MDD controlled studies, the incidence of euphoria-related AEs was low for ALKS 5461 2mg/2mg and PBO (1.6% vs 0.2%, respectively) and there was no evidence of dependence or withdrawal. No patients randomized to ALKS 5461 reported abuse behavior AEs.

Conclusions: These findings indicate that SAM mitigates the abuse potential of BUP in the ALKS 5461 2mg/2mg combination.

Supported By: Alkermes, Inc.

Keywords: Abuse Potential, Physical Withdrawal, Buprenorphine, Samidorphan, Opioid Antagonist

F173. Negative Trial of Scopolamine in Major Depressive Disorder Does Not Demonstrate Neurophysiological Changes Seen With the Antidepressant Response of Ketamine

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Background: There is considerable evidence supporting the importance of the muscarinic cholinergic system in the regulation of mood symptoms. A number of studies have demonstrated significant and relatively rapid improvement in depression with the administration of IV or PO scopolamine. The purpose of this study is to conduct a randomized controlled cross over trial of IV scopolamine vs. placebo to determine its clinical efficacy in unipolar depression. In addition, we hope to compare the effects of scopolamine on neurophysiological markers (BDNF and MEG gamma power) with another rapid acting antidepressant (ketamine).

Methods: This was a randomized placebo-controlled crossover trial of 23 individuals with current diagnosis of Major Depressive Disorder. Following a 2 week med free period and single-blind placebo lead-in, participants were randomized to receive two counterbalanced blocks of three intravenous infusions of scopolamine (4 ug/kg) and placebo infusions. Block order was randomized. Clinical outcome measures included the MADRS and HAM-A. In addition to clinical measures, MEG and serum BDNF were obtained at baseline and after each treatment phase.

Results: No significant effect of scopolamine was seen on depression (compared to placebo). Secondary analysis demonstrated a greater effect size for patients with a greater number of past treatment trials (though overall effect sizes were quite small). No significant drug versus placebo effects were seen in MEG gamma power or BDNF levels.

Conclusions: Contrary to previously investigations, these results do not support the use of scopolamine for depression.

This study provides no evidence that scopolamine and ketamine gain efficacy via a shared mechanism of action.
Supported By: NIMH intramural
Keywords: Scopolamine, Depression, Ketamine, MEG, BDNF

F174. Higher Baseline Plasma Serotonin, and a Greater Decrease in Serotonin Over Treatment, is Associated With Better SSRI Response in MDD

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Background: The exact mechanisms of SSRIs are unclear despite extensive research. Previous studies show an association between serotonin levels at baseline and treatment efficacy in MDD, but results are conflicting. In this study we explored the association between plasma levels of serotonin and antidepressant treatment response in MDD subjects undergoing open-label treatment with an SSRI.
Methods: 23 MDD subjects (15 women, 8 men, ages 21 -65 years), who had been medication-free for at least 6 weeks, were treated with an SSRI for 8 weeks. Plasma serotonin levels were measured pre- and post -treatment using ultra HPLC/tandem MS and GC/MS. Treatment response was defined as a $\geq$50% decrease on the Hamilton Depression Rating Scale.
Results: SSRI Responders (n=16) had significantly higher serotonin levels at baseline compared to SSRI Non-responders (n=7) (t=-2.7, p=0.01). There was no significant difference between serotonin levels after 8 weeks of treatment in Responders vs Non-responders (t=0.63, p=0.53). In all subjects, there was a significant decrease in serotonin levels between baseline and week 8 (t=6.2, p=0.000003). The decrease was more prominent in Responders (t=5.9, p=0.00003) than in Non-responders (t=3.0, p=0.03).
Conclusions: We found that MDD subjects who responded to treatment with an SSRI had significantly higher baseline serotonin levels compared to those who did not respond, and that serotonin levels significantly decreased with treatment in all subjects, but more prominently in the Responders. This finding could lead to a greater understanding of the mechanisms of SSRI efficacy, and to new possibilities of predicting SSRI treatment response.
Supported By: This study was funded by grants from the National Institute of Mental Health (NIMH; grant No. R01-MH083784), the O'Shaughnessy Foundation, the Tinberg family, the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC), and the Bernard and Barbro Foundation. This project was also supported by the National Institutes of Health/National Center for Research Resources (NIH/NCRR) and the National Center for Advancing Translational Sciences, NIH (through UCSF-CTSI grant No. UL1 RR024131).

Daniel Lindqvist was supported by the Swedish Research Council (registration number 2015-00387), Marie Sklodowska Curie Actions, Cofund (Project INCA 600398), the Swedish Society of Medicine, the Söderström-Königska Foundation, the Sjöbring Foundation, OM Persson Foundation and the province of Scania (Sweden) state grants (ALF).
Keywords: Major Depressive Disorder (MDD), Antidepressants, Biomarkers, Selective Serotonin Reuptake Inhibitors, Serotonin

F175. Cyclooxygenase-2 Inhibitor Combination Treatment Reduces Plasma C-Reative Protein Levels in Bipolar Depression

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Background: Neuroinflammation appears to play key roles in the pathophysiology of bipolar depression (BDD). Many patients diagnosed with stress-related mood disorders have increased levels of pro-inflammatory mediators, such as C-reactive protein (CRP). This is the first study to analyze CRP levels in bipolar disorder patients treated with the cyclooxygenase-2 inhibitor, celecoxib (CBX).
Methods: In this randomized, double-blind, two-arm, placebo-controlled study, 47 patients with BDD received either the SSRI escitalopram + CBX, or escitalopram + placebo. Plasma CRP levels were measured in both groups at 3 times points, and in a healthy control (HC) group. CRP concentrations were measured using sandwich ELISA, and depression levels were quantified using the Hamilton Depression Scale (HAMD-17).
Results: The CBX group had significantly lower HAMD-17 scores vs. placebo at week 4 (P=0.026) and week 8 (P=0.002). Baseline CRP levels were significantly increased amongst BDD patients versus HC subjects (P=0.044). No significant differences in CRP levels were measured between CBX and placebo groups at baseline (P=0.156), but by week 8 CRP was significantly decreased in the CBX group vs. placebo (P=0.003). Positive correlations were measured between CRP vs. IL-6.
Conclusions: SSRI + CBX combination is more effective than SSRI + placebo in reversing treatment resistance and augmenting antidepressant response in BDD. CRP may be a useful biomarker for BDD, evidenced by its elevated plasma levels in BDD patients vs. HC subjects. Since CRP decreased significantly with CBX treatment compared to placebo, CRP may be a useful biomarker for monitoring treatment response in BDD patients during SSRI + CBX treatment.
Supported By: Stanley Medical Research Institute (SMRI)
Keywords: Bipolar Disorder, Celecoxib, C-reactive Protein, Treatment Resistance, Neuroinflammation

F176. A Randomized, Double-Blind, Placebo-Controlled-Crossover Design Investigating the Impact of a Pharmacological Challenge on Neural Mechanisms of Response Inhibition in Depression

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Background: Lurasidone, a D2 antagonist with anti-depressant properties, has been found to be effective at reducing depressive symptoms in bipolar disorder and depression with mixed features. Despite its therapeutic benefits, little is known about the effects of lurasidone on neural processes in depression. Deficits in response inhibition (RI) are implicated in depression and persist beyond episodes. The current study examined the effects of lurasidone on neural mechanisms of RI in depression.
Methods: An acute dose of lurasidone (20mg) was administered to 39 adults (18-25) across the spectrum of depressive symptomology in a randomized double-blind, placebo-controlled-crossover design. Participants completed a Stop Signal Task (SST) during fMRI after receiving placebo and lurasidone, one week apart, in a randomized order.
Results: Cluster-corrected whole-brain analysis identified a significant symptom by drug by task condition interaction in the left parietal operculum (PO; k=145, MNI: -40,-24,16). Negative PO activity was observed during successful inhibitions, relative to go trials. However, a positive association between depression severity and activity in this region was found, such that individuals with greater depressive symptomology had less differentiation between PO response during action execution and inhibition on lurasidone, but not placebo (difference: z=3.21, p<.01).
Conclusions: In the SST, the PO demonstrated a negative response while inhibiting. As such, normative function may be to suppress activity in this region during inhibition of a prepotent action. Reduced suppression of PO activity during inhibition on lurasidone with increasing depression severity could be indicative of aberrant RI mechanisms in depression that were evident as the result of a pharmacological challenge.
Supported By: Wellcome Trust and Biomedical research Centre
Keywords: Brain Imaging, fMRI, Atypical Antipsychotic Drug, Depressive Symptoms, Response Inhibition, Stop-Signal Task

F177. Pharmacogenomics of Serotonin Noradrenergic Reuptake Inhibitors (SNRIs) Antidepressant Response After Selective Serotonin Reuptake Inhibitors (SSRIs) Treatment Failure in Major Depressive Disorder

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Background: This study was conducted to investigate the pharmacogenomics of antidepressant treatment-associated remission during treatment with serotonin noradrenergic reuptake inhibitors (SNRIs), either duloxetine or venlafaxine, in depressed patients who had failed treatment with selective serotonin reuptake inhibitors (SSRIs).
Methods: Data sources for these analyses include data from two clinical trials: the Pharmacogenomic-Research-Network (PGRN) Antidepressant-Medication-Pharmacogenomics-Study (AMPS) and the Sequenced-Treatment-Alternatives-to-Relieve-Depression (STAR*D) study. In the PGRN trial, patients were offered 8 weeks of treatment with duloxetine (N=145 enrolled, N= 57 analyzed). In the STAR*D trial, patients were offered Level 2 treatments including venlafaxine (N=250 enrolled, N= 82 analyzed). This analysis focused on both pharmacokinetic (PK, i.e., cytochrome p450 CYP2D6, 2C9, CYP2C19) and pharmacodynamic (PD, i.e., serotonin and norepinephrine transporters) genetic variation hypothesized to contribute to SNRI treatment remission.
Results: Venlafaxine remission rates were higher among ultra-rapid metabolizers (URM) (71.4% remitted) than among CYP2D6 poor metabolizers (PM) (10% remitted). Assuming a linear effect of CYP2D6 metabolizer status on venlafaxine remission higher metabolism was associated with greater odds of remission [OR = 4.7, p = 0.018]. Further, venlafaxine remission was associated with an interaction between SLC6A4 5-HTTLPR L/L genotype and CYP2D6, when URM was compared with IM/EM (p=0.021). A similar interaction effect on remission was observed between CYP2D6 URM and NET G1287A G/A genotype (p = 0.021).
Conclusions: Metabolizer status resulting from CYP2D6 genetic variation may contribute to SNRI treatment remission in MDD patients. Replication of these findings in a larger sample, particularly from the standpoint of PK-PD interactions and treatment remission is warranted.
Supported By: Funding: Research reported in this abstract was supported by National Institute of General Medical Sciences of the National Institutes of Health under award number T32 GM008685.
Keywords: Major Depressive Disorder (MDD), Pharmacodynamic-Pharmacokinetic Interaction, CYP2D6, SLC6A4, NET, Venlafaxine, Remission

F178. High Functioning Autism Spectrum Disorder Shows Normal Task-Related Neural Activity but Altered Functional Connectivity During a Spatial N-Back fMRI Task

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Background: Executive function (EF) deficits in patients with autism spectrum disorder (ASD) are ubiquitous and understudied. We performed functional neuroimaging using an N-back spatial working memory task known to reliably activate fronto-parietal networks related to working memory. Functional connectivity of working memory networks was examined and related to executive function performance in participants with ASD and healthy controls (HC).

Methods: Neuroimaging was acquired in n=40 participants with ASD without comorbid intellectual disability and n=20 HC (ASD, mean age=23±10; HC, mean age=23±9). Participants performed a visuospatial N-back task consisting of a 0-back and 2-back condition during scanning. Measures of clinical symptoms and CANTAB EF measures were also collected. Task-based fMRI analyses were carried out using SPM12, and Generalized Psychophysiological Interactions(gPPI) were used to examine dorsolateral prefrontal cortex (DLPFC) functional connectivity in participants with ASD versus HC. Permutation analysis was used (FSL's PALM) to determine TFCE corrected p-values.

Results: N-back task performance activated fronto-parietal and deactivated default mode networks in ASD and HC ($p<0.05$ TFCE corrected). Between-group differences in task-related connectivity to the left DLPFC were found in ASD, specifically short-range over-connectivity during 0-back, and reduced contralateral connectivity during 2-back. Task connectivity in ASD was related to N-back reaction time, but not to ADOS scores or CANTAB stop-signal reaction time or spatial working memory tasks.

Conclusions: Participants with ASD without intellectual disability showed normal task-related activity but deficits in functional connectivity during spatial working memory performance. Altered connectivity in ASD related to N-back task performance but not out-of-scanner EF tasks or clinical symptoms.

Supported By: Ontario Mental Health Foundation

Keywords: High-functioning Autism, Executive Function, Working Memory fMRI, Functional Connectivity, Fronto-Parietal Network

F179. Epigenetic Biomarkers in Women With Posttraumatic Stress Disorder After CRF1 Receptor Antagonist Treatment

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Background: In a unique placebo controlled randomized clinical trial we have previously evaluated the efficacy of a novel CRF1-antagonist (GSK561679) in female PTSD patients. We identified a specific subgroup of patients with significantly better treatment response to the drug, i.e. patients with child abuse and carriers of the GG-genotype of the CRHR1 SNP rs110402. Extending our previous study, we now investigated epigenetic biomarkers within PTSD-relevant genes and their association with GSK561679 treatment response in both the entire cohort and the relevant subgroup.

Methods: We analyzed genotypes and DNA methylation levels from peripheral blood and measured multiple psychological assessments in the same cohort of PTSD-diagnosed women treated with GSK561679 (N=43) or placebo (N=45).

Results: In particular, we measured baseline and post-treatment methylation levels in CRHR1, NR3C1 and FKBP5. We observed significant differences in CRHR1 methylation after GSK561679 treatment in the subgroup of patients with better treatment response (n=28; p=0.00005). Furthermore, NR3C1 baseline methylation levels significantly interacted with child abuse to predict PTSD symptom change following GSK561679-treatment (n=78; p=0.044).

Conclusions: Taken together, these results reveal a possible role of epigenetic biomarkers in CRHR1 to track response to GSK561679-treatment in biologically relevant subgroups. We further support previous findings showing pre-treatment NR3C1 methylation levels to predict PTSD treatment outcome, independent of the type of therapy. To analyze functionally relevant CpG sites that could specifically serve as epigenetic biomarkers, targeted bisulfite sequencing experiments of the entire FKBP5 locus are under way with special focus on CpGs located in putative enhancer regions, as these sites are less well covered in the Illumina-arrays.

Supported By: NIMH, Max- Planck-Institute of Psychiatry, GlaxoSmithKline

Keywords: PTSD - Posttraumatic Stress Disorder, Epigenetic Biomarkers, DNA Methylation, CRHR1 Antagonist, FKBP5

F180. Spontaneous Eye Blink Rate: A Good Proxy for Dopamine?

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Background: Dopamine is central to a number of cognitive functions and brain disorders. Given the cost of neurochemical imaging in humans, behavioral proxy measures of dopamine have gained in popularity in the past decade, such as spontaneous eye blink rate (sEBR). Increased sEBR is commonly associated with increased dopamine function based on pharmacological evidence and patient studies. Yet, this hypothesis has not been validated using in vivo measures of dopamine function in humans.

Methods: In order to fill this gap, we measured sEBR using electro-oculography, and striatal dopamine synthesis capacity using [18F]DOPA PET, in 20 participants (9 healthy individuals and 11 pathological gamblers).

Results: In contrast to our prediction, frequentist statistics indicated a negative relationship between sEBR and dopamine synthesis capacity (Spearman ρ=-0.504, p=0.024). Given the unexpectedness of this finding, we used Bayesian statistics to quantify the evidence for the null hypothesis that sEBR and dopamine synthesis capacity are not positively correlated. The relative evidence for the null

hypothesis was strong (Bayes factor: BF01=10.34), indicating that our data are ten times more likely under the null hypothesis of no positive relationship than under the alternative hypothesis of a positive relationship. Finally, an exploratory voxel-wise analysis showed that the negative relationship between sEBR and dopamine synthesis capacity was strongest in the left nucleus accumbens.

Conclusions: These results, which complement findings from a recent study that failed to observe a relationship between sEBR and dopamine D2 receptor availability, suggest that caution and nuance are warranted when interpreting sEBR as a proxy measure of striatal dopamine.

Supported By: Netherlands Organisation for Scientific Research (NWO); James McDonnell Foundation

Keywords: Dopamine, Spontaneous Eye Blink Rate, Positron Emission Tomography, FDOPA

F181. Association of Plasma Nitrite Levels With Metabolic Syndrome and its Components in the Old Order Amish

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Background: Metabolic Syndrome (MetS), a constellation of major cardiovascular risk factors, is highly prevalent in mental illness, thereby increasing morbidity and mortality. NO/nitrite pathways have been previously associated with obesity/ metabolic syndrome but the direction of association remains inconsistent, probably due to sample heterogeneity. We now hypothesized that, in the Old Order Amish, a relatively homogeneous population, nitrite levels will be higher in obesity and MetS.

Methods: Fasting nitrite levels were measured in a convenience sample of 116 Old Order Amish, (78.4% females) and related to existing metabolic data. We performed age and sex adjusted three-way ANCOVAs analyses with Bonferroni bivariate tests to compare nitrite levels between the three groups, a) Obese/overweight(+)MetS(-), b)Obese/overweight(+) MetS(+) and c) Obese/overweight(-). Linear multivariate regressions were also used for individual continuous metabolic variables.

Results: A significant effect of BMI-category was identified $F(2, 109)=14.97, p<0.0001$). A higher nitrite level was found in the Obese/overweight(+)MetS(+) group than the other two groups ($p=0.001$) and in the a)Obese/overweight(+)MetS(-), group relative to the normal weight group ($p=0.016$). After adjusting for age and sex, we found a significantly positive relationship between nitrites and BMI, triglycerides, HDL/ Cholesterol ratio, blood glucose and a negative relationship with HDL-C levels ($p< 0.0001$ for all analyses). No significant association was found with blood pressure, waist and hip circumference, LDL-cholesterol and CRP.

Conclusions: If confirmed in larger longitudinal studies, plasma nitrite levels may serve as predictors and even molecular targets for Obesity/ MetS, major risk factors for cardiovascular morbidity and mortality in general, as well as in psychiatric populations.

Supported By: Study supported by a NORC exploratory grant (PI Postolache), offspring of the parent grant P30 DK072488 and the University of Maryland, Joint Institute for Food Safety and the Applied Nutrition JIFSAN/ FDA cooperative agreement FDU.001418.

Keywords: Metabolic Syndrome, Cardiovascular Disease, Nitric Oxide

F182. Daydreaming and Depression: The Response to Stimulants

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Background: Daydreaming is common in both childhood and adulthood. In children with ADHD, inattentive type particularly, it contributes to their distractibility. Stimulants are the standard treatment for ADHD, but there is no data on the preferential benefit of stimulants for depressed adults who also frequently daydreamed as children.

Methods: A retrospective chart review was performed on patients in a private outpatient psychiatric clinic. Data collected included demographics, medication history, answers to how frequently they daydreamed in school, PHQ-9 scores from every visit, and their current diagnoses.

Results: Over a three-year period, 217 patients completed the initial questionnaire. Of these, 80 reported they had daydreamed “frequently” or “continuously” as a child. Clinical depression was diagnosed in 67% of the continuous daydreamers, 44% of the frequent daydreamers and 23% of those who never daydreamed. ADD was diagnosed in 38% of the continuous daydreamers, 32% of frequent daydreamers, and 16% of occasional or never daydreamers. When the

continuous daydreamers were treated with stimulants, their depression remitted more effectively as measured by most recent PHQ-9 score (5.8 vs. 12.9, p<.08, PHQ at intake of 16.4).
Conclusions: Childhood daydreamers in this patient population were more likely to be diagnosed with depression in adulthood and more likely to respond to stimulants. There is increasing awareness that overlapping symptoms of what appear to be unrelated diagnoses may have the same biological origins and may thus respond to the same treatments. This data raises the possibility that there is shared neurocircuitry between daydreaming in childhood and later onset of depression.
Keywords: Stimulants, ADHD, Daydreaming, MDD

F183. Synergism Between Immune-Driven Illnesses and TBI Predicts Suicidal Behavior: A Danish Registers Based Study

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Background: Immune activation before and after traumatic brain injury (TBI) worsens its prognosis. Both TBI and inflammation have been predictively associated with a higher risk of suicidal behavior. Immune-mediated conditions (IMCs, such as allergic, infectious and autoimmune diseases) lead to low-grade immune activation. In this study, we capitalize on the robust capabilities of the Danish registers to estimate interactions between history of immune-mediated clinical conditions (infections, allergy and autoimmune) and traumatic brain injury (TBI) future predicting future suicidal self-directed violence (SSDV).
Methods: All 7.22 million individuals- 15 years or older living in Denmark between January 1, 1980, and December 31, 2011, were observed during a 32-year follow-up period, with more than 149 million person-years of follow-up. During the follow-up period, 32,683 suicides were observed. Death, medical, psychiatric, demographic data were obtained from the specific Danish registers. Statistics included logistic regressions, adjusted for age and sex, and then stratified by sex.
Results: There was a significant interaction between TBI and IMCs in predicting SSDV- with more-than-additive effects for infections and allergy (p<0.001), and less-than-additive effects for autoimmune disease (p<0.001). This interaction did not differ between genders, and was robust for adjusting or stratifying by history of mood disorders.
Conclusions: These novel results confirm potentiating interactions between TBI and certain IMCs (infections and allergy, but not autoimmune conditions) in predicting SSDV. Future work involves adjustment for demographic, socioeconomical and psychiatric factors potentially involved in vulnerability and resilience to SSDV in Denmark, and investigating possible molecular mediation.
Supported By: Funded with an unrestricted scholarship grant from the Lundbeck Foundation. Dr. Postolache was additionally supported by a Distinguished Investigator Award from the American Foundation for Suicide Prevention and intramural funds from the Rocky Mountain MIRECC for Suicide Prevention.
Keywords: Traumatic Brain Injury, Suicidal Behavior, Infections, Allergy, Autoimmune Conditions

F184. Methylenetetrafolate Reductase (MTHFR C677T) Gene Polymorphism and Depression: A Community Based Study From Rural North India

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Background: Depression is one of the major public health concerns, which is majorly unexplored, neglected, under diagnosed among population of rural areas of India. The present study attempts to understand the prevalence and causes (social and genetic) of depression among rural population of North India.
Methods: A door to door survey has been conducted to recruit 808 individuals, aged 30+ years from the Palwal District of Haryana (India), on which data pertaining to demographic characteristics was taken. Written consent was taken from the recruited individuals after explaining the merits and demerits of the study. All the individuals have been screened for depressive symptoms using Becks depression inventory (BDI II). MTHFR C677T gene polymorphism was analysed by Polymerase chain reaction (PCR) amplification followed by restriction digestion with Hinf I. SPSS version 20 has been used to analyse the results.
Results: Of the total recruited individuals, 31.1% of the individuals were found to be suffering from depression (18.6% mild depression, 10% moderate depression and 2.5% severe depression). Females were found to be significantly more depressed (35.7%) than males (24.6%)- p<0.001. Female gender, Illiteracy, and unemployment were found to be significant cofactors for moderate/ severe depression. No association was found between MTHFR C677T gene polymorphism and depression among the studied population; however, the distribution of T allele decreased in cases than normal which means that T allele is lethal for depression.
Conclusions: No association was found between MTHFR C677T gene polymorphism and depression controlling all the social factors in the studied population of North India.

Keywords: Depression, Methylenetetrafolate Reductase Gene Polymorphism, Social Factors

F185. A History of Concussion Predicts Brain Chemistry Changes in NCAA Division I College Athletes

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Background: Sports-related concussion (SRC) is thought to be associated with brain chemistry alterations, involving the neuronal viability marker N-acetyl aspartate (NAA). SRC is common in basketball, yet few studies have focused on this sport. This study's aim was to investigate the impact of both historical and prospectively-occurring SRC on neurometabolites including NAA, in college basketball players, before and after a season of play.
Methods: 30 University of Utah basketball players were enrolled. Using a 3 Tesla MRI system, Proton-1 magnetic resonance spectroscopy scans were acquired, before and after the 2015-2016 Pac-12 season. Participants were divided into those with and without a prior history of SRC, and were monitored during the season for new-onset concussion. Mood and affect symptoms were measured using the Profile of Mood States (POMS).
Results: 11 participants had a history of SRC; 19 participants did not. During the season, 1 participant experienced a SRC. At baseline, there was no difference in cortical NAA between the 2 groups. However, at the post-season scan, we observed lower NAA in the right dorsal anterior cingulate cortex (dACC) in players with a history of SRC (9.40±0.43) relative to players without SRC (9.85±0.52; p=0.04). In addition, dACC NAA was positively correlated with the Vigor-Activity Subscale of the POMS.
Conclusions: These findings suggest a prior history of SRC may serve as a moderator of dACC NAA in college basketball athletes. This study is ongoing, and will prospectively measure changes in brain microstructure and chemistry associated with SRC in our sample.
Supported By: PAC-12 Wellness Grant; USTAR
Keywords: Sport-Related Concussion, Basketball Player, MRS, NAA

F186. Common Non-Behavioral Clinical Features of Anti-NMDAR Encephalitis Presenting as a Psychiatric Disorder

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Background: Diagnosing anti-NMDA receptor encephalitis (anti-NMDArE) can be challenging because it often presents in the form of a primary psychiatric disorder, and approximately three-fourths of patients are first evaluated by a psychiatrist. Prompt and effective treatment can avert serious long-term disability or death, but timely intervention requires early recognition. Descriptions of a prototypical episode have been published, but there is enormous variability between patients with respect to how the illness course evolves. Greater awareness of its salient clinical features could promote earlier accurate diagnosis.
Methods: A systematic search of PubMed and EMBASE databases was performed to identify published reports of adult anti-NMDArE cases with behavioral or psychiatric symptoms. Duplicate reports were eliminated by manual review.
Results: Forty-five unique male patients (mean(S.D.) age 36.5(15.9) years) and 185 female patients (mean(S.D.) age 29.4(10.3) years) were identified. Seizures were the most frequently reported features (61.3%), followed by disorientation/confusion (42.6%), orofacial dyskinesias (39.1%), mutism/staring (37.0%), dyskinesias of other body parts (36.6%), memory disturbance (34.5%), diminished arousal (30.2%), fever (28.1%), and language disturbance (26.0%).
Conclusions: In published reports of anti-NMDArE cases likely to be first evaluated by a psychiatrist, the most commonly observed clinical features are not ordinarily associated with primary psychiatric disorders. Awareness of these diagnostic clues, coupled with heightened clinical vigilance, should reduce the likelihood of a misdiagnosis.
Keywords: NMDA Receptor, Autoimmune Disorder, Diagnosis

F187. Hippocampal Activation During Inhibition Predicts PTSD: A Prospective Emergency Department Study

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Background: Impaired inhibition of fear or behavioral responses is thought to be central to PTSD symptomatology. Recent studies have shown the significance of hippocampal functioning in this context; however, prospective studies are needed to understand its role in resilience versus the development of PTSD in the immediate aftermath of trauma.
Methods: Trauma survivors who were brought to the Emergency Department were enrolled in the study. Both an original sample (N=27) and a replication sample (N=31) performed a Go/NoGo task in a 3T scanner 1-2 months post-trauma. A subset (N=28) returned for a second scan during which a fear conditioning and extinction paradigm was conducted.
Results: Elastic net regression was used to define the most optimal model predicting future PTSD in the original sample. Hippocampal activation during response inhibition significantly predicted PTSD at 3 months (F(11,22)=4.33, p=0.01) and 6 months post-trauma (F(9,19)=4.96, p=0.01). This finding was confirmed in the replication sample (3 months, F(3,23)=3.03, p=0.05; 6 months, F(3,20)=5.74, p=0.007). Second, hippocampal activation during fear conditioning correlated positively with resilience score measured at time of scan (r=0.48, p=0.01). Furthermore, reduced hippocampal activation during context-dependent fear extinction was found in individuals who met DSM-IV criteria for PTSD 3 months post-trauma

compared to the trauma-exposed controls (t(22)=2.16, p=0.04).

Conclusions: We demonstrate that inhibition-related hippocampal functioning predicts future PTSD symptoms, and show the importance of the hippocampus in promoting resilience in the early aftermath of trauma. These studies reveal hippocampus-dependent functioning as a potential biomarker for PTSD development and interesting target for early interventions.

Supported By: R01 MH094757 (to KJR), R21 MH106902 (to TJ), F32 MH101976 (to JSS); GT/GSU Center for Advanced Brain Imaging Seed Grant (SVR)

Keywords: PTSD - Posttraumatic Stress Disorder, Fear Conditioning and Inhibition, Resilience, Predictive Biomarkers, Brain Imaging, fMRI

F188. Preliminary Evidence for mGluR5 Dysregulation in Borderline Personality Disorder and Relationship to Suicidal Behavior

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Background: Borderline Personality Disorder (BPD) is a debilitating psychiatric condition, associated with 75% lifetime suicide attempt and 10% suicide mortality. However, relatively little is known about the pathophysiology of BPD on a molecular level. The metabotropic glutamate receptor type 5 (mGluR5) may play a role in the pathophysiology of both BPD and suicidal behavior given its role in emotion regulation, social and cognitive functioning, and pain processing. This study examined the relationship between mGluR5 availability, BPD, and suicidal behavior in vivo.

Methods: Twenty individuals with MDD, 9 of whom had comorbid BPD, and 20 age-, sex-, and smoking-matched healthy comparison controls (HC) participated in an [18F]FPEB PET scan and clinical assessment. Volume of distribution (VT: ratio of parent radioligand concentration in tissue relative to that in blood) was the outcome measure.

Results: We observed significantly higher mGluR5 VT in individuals with BPD compared to both MDD only and HC participants across brain regions implicated in the neurobiology of BPD [(amygdala; 32% higher, p<.001), dorsolateral PFC (24% higher, p=.015); and orbitofrontal cortex (29% higher, p=.002)]. In the BPD, but not MDD only group, higher mGluR5 VT was also associated with history of suicide attempt across regions of interest (28-33% higher, p's=.002-.046).

Conclusions: This is the first in vivo investigation implicating mGluR5 dysregulation in BPD. Importantly, higher mGluR5 availability was associated with history of suicide attempt in individuals with BPD. Larger studies are warranted; however, findings suggest mGluR5 may be a critical treatment target for BPD, and suicidal behavior in this disorder.

Supported By: R01MH113868

Keywords: Borderline Personality Disorder, mGluR5, PET Imaging, Suicide Attempts, Major Depressive Disorder (MDD)

F189. Heart Rate Variability During a Cognitive Reappraisal Task in Borderline Personality Disorder: The Role of Comorbid Posttraumatic Stress Disorder and Acute Dissociation

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Background: High-frequency heart rate variability (HF-HRV) is a reliable measure of autonomous nervous system functioning, with lower HF-HRV being linked to more difficulties in stress regulation. Emotion dysregulation is a core feature of Borderline Personality Disorder (BPD). However, previous research on HF-HRV in BPD has revealed mixed findings; the role of comorbid Posttraumatic Stress Disorder (PTSD), medication status, and acute dissociation in this context remains unclear. This study aimed to investigate HF-HRV during resting-state versus an emotion regulation task in BPD patients with comorbid PTSD (BPD+PTSD), patients without this comorbidity (BPD), and healthy controls (HC).

Methods: 57 patients (BPD+PTSD: n=20, BPD: n=37) and 27 HC performed an emotion regulation task with neutral, positive, and negative images, while electrocardiogram data and arousal ratings were assessed. Participants were instructed to either attend or down-regulate their emotions using cognitive reappraisal.

Results: Both BPD and BPD+PTSD reported higher arousal during the emotion regulation task than HC (F(2,81)= 6.36, p=.003), while HF-HRV was only reduced in BPD+PTSD (F(2,80)= 6.69, p=.002). Medication status had no significant effect on HF-HRV (all p>.05). However, acute dissociation significantly interacted with instructed emotion regulation in BPD (F(1,48)= 4.73, p=.035): patients with higher dissociation showed higher HF-HRV for down-regulating versus attending negative pictures (F(1,48)= 7.53, p=.008).

Conclusions: These novel un-published findings suggest that lower HF-HRV in BPD is related to comorbid PTSD, which may worsen difficulties in stress regulation. Acute dissociation may be a regulatory strategy to cope with negative emotions in BPD. Further implications for future research and the clinical setting are discussed.

Supported By: German Research Foundation (Clinical Research UnIt KFO256)

Keywords: Heart Rate Variability, Borderline Personality Disorder, Posttraumatic Stress Disorder, Emotion Regulation, Dissociation

F190. Hippocampal Subfield Activity May Mediate Aspects of Psychosis

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Background: Although psychosis is the defining and the most recognizable symptom domain in schizophrenia, the biological mechanism underlying psychosis remains unknown. Analysis

of post-mortem human hippocampal tissue and in vivo human imaging studies in schizophrenia have detected abnormalities within hippocampal subfields: decreased GluN1 within the dentate gyrus (DG), increased synaptic plasticity markers in CA3, and increased basal activity within CA3 which correlate with psychosis severity. However, a causal link between this hippocampal dysfunction and psychosis has yet to be determined. Therefore, we sought mouse preparations which recapitulate this pathology.

Methods: First, we utilized a genetic mouse model which lacks GluN1 selectively in the DG. Next, we infused mice with AAVs containing DREADDs to activate CA3 or inhibit DG, allowing manipulation of activity with spatial, temporal, and cell-type specificity. We then assessed the behavioral phenotypes of these preparations, utilizing paradigms associated with a psychosis-like phenotype: prepulse inhibition, fear conditioning, and social memory, and assessed how these changes affect basal activity both within the hippocampus as well as in afferent brain regions.

Results: Reduction of GluN1 in DG impairs PPI and social memory and potentiates fear conditioning, and induces homeostatic upregulation of cellular excitability within CA3. Meanwhile, activation of ventral CA3 enhances contextual fear conditioning, while activation of the dorsal CA3 impairs social memory. Analysis of the effects of DG inhibition is currently underway.

Conclusions: Results suggest that different aspects of a psychosis-like phenotype are affected by activity along the longitudinal axis of the hippocampus, suggesting novel therapeutic targets based upon symptomatology.

Supported By: NARSAD

Keywords: Model Psychosis, Hippocampus, DREADDs, NMDA Receptor, Animal Model

F191. Maternal Immune Activation Models: Mind Your Caging Systems!

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Background: The poly(I:C) model is one of the most widely used model of maternal immune activation (MIA). While it is known that the effects of MIA can be influenced by various factors, it has been largely ignored so far, whether differences in housing can also affect the outcomes in the offspring. Here, we examined this possibility by comparing poly(I:C)-based MIA in two housing systems, namely individually ventilated cages (IVC) and open cages (OC).

Methods: Mice, kept in IVC or OC, were treated with a low (1 mg/kg, i.v.) or high (5 mg/kg, i.v.) dose of poly(I:C) or vehicle, on gestation day (GD) 9 or 12. Offspring were maintained in IVC or OC until adulthood for behavioral testing. The influence of housing on poly(I:C)-induced cytokine responses (maternal and fetal compartments, 1 and 6 hrs post-treatment) was assessed in an additional cohort of dams.

Results: Poly(I:C) administration on GD9 caused a dose-dependent increase in abortion in IVC but not in OC, whereas MIA in IVC at GD12 did not do so. Cytokine responses to poly(I:C) were higher in animals kept in IVC as compared to OC. The efficacy of MIA to induce long-term behavioral deficits was influenced by housing, poly(I:C) dosing, and prenatal timing.

Conclusions: The present study identified the housing system as a novel factor that can confound the outcomes of MIA. Our findings thus urge the need to consider and report the kind of cages used in rodent MIA models. Providing this information seems pivotal to yield robust and reproducible results in these models.

Supported By: SNF

Keywords: Maternal Immune Activation, Neurodevelopmental Disorders, Reproducibility

F192. Optogenetic Inhibition of Parvalbumin-Positive Interneurons in Mice as a Model for Neural Network Dysfunction in the Medial Prefrontal Cortex

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Background: Parvalbumin-positive interneurons are crucial for neural network gamma oscillations, which can be analyzed using EEG recordings and auditory stimulation. It was shown that patients with schizophrenia exhibit deficits in auditory event related oscillations. We used EEG in combination with optogenetics in the prefrontal cortex of mice to test the hypothesis that parvalbumin-positive interneurons are involved in gamma oscillations and auditory stimulus processing.

Methods: We expressed a light activatable proton pump (Arch) in parvalbumin-positive interneurons of parvalbumin-Cre mice. Mice were implanted with recording electrodes and an optic fiber for interneuron inactivation. After recovery, mice were subjected to auditory stimulation (600 x 10 ms, 80 dB white noise clicks) in a sound attenuated chamber. The light was turned on in 50% of trials at time -1.5 to 0.5 s from stimulus onset.

Results: Upon light inhibition, two of the three mice showed a low current in their local field potential, indicating a low expression of Arch or low number of Arch expressing neurons. In these mice, basal gamma power was decreased ($n=15$ and 16 electrodes/mouse, $p<0.0001$, two tailed paired t test). A third mouse displayed a strong inhibitory current and showed decreased evoked gamma power ($n=16$, $p<0.0001$). Basal gamma was unaffected in all mice.

Conclusions: These preliminary results show that inhibition of parvalbumin-positive interneurons affects processing of auditory stimuli. The different results between mice probably reflect the variability of Arch expression. Other stimulation paradigms (e.g. ASSR) will be performed and corroborated with histological analysis to determine the extent of Arch expression and electrode position.

Keywords: Auditory Stimulation, Auditory Evoked Potential, Parvalbumin, Gamma Oscillations, Optogenetics

F193. Overexpression of NOS1AP in Dorsal Hippocampus and Medial Prefrontal Cortex Induces Schizophrenia-Related Phenotypic Changes

Esin Candemir[1], Nikolai Fattakhov[1], Li-Li Li[2], Xufeng Chen[3], Dilhan Esen[1], Veronika Frerichs[1], Saleha Arshad[1], Lena Grünewald[1], Aet O'Leary[1], David A. Slattery[1], Jakob von Engelhardt[3], Michael J. Courtney[2], Andreas Reif[1], and **Florian Freudenberg**[1]

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Background: Neuronal nitric oxide synthase (nNOS) and its adaptor protein (NOS1AP) have been implicated in schizophrenia. Elevated NOS1AP levels have been reported in schizophrenia patient and schizophrenia-like neuronal alteration have been shown by NOS1AP overexpression in vitro. Here we investigated functional and mechanistic consequences of NOS1AP overexpression in vivo with regards to phenotypes related to schizophrenia and comorbid conditions.
Methods: We stereotaxically targeted the medial prefrontal cortex (mPFC) or dorsal hippocampus (dHpc) of adult C57Bl/6J mice (N=14-15/group) using recombinant adeno-associated viruses expressing NOS1AP or mCherry (control). Four weeks post-surgery, mice were behaviorally characterized or killed for molecular and histological characterization.
Results: A ~10-fold increase in NOS1AP mRNA and protein was confirmed by qRT-PCR and immunoblotting. Social interaction was impaired by NOS1AP overexpression in dHPC (P=0.038; mPFC: P=0.829), while social memory was unaffected (mPFC: P=0.224; dHPC: P=0.987). NOS1AP overexpression in mPFC (P=0.047), but not dHPC (P=0.316), impaired spatial working memory. Additionally, open arm time in the elevated zero maze was reduced by NOS1AP overexpression in dHpc (P=0.041), and increased, though not significantly, in mPFC (P=0.168). NOS1AP overexpressing neurons in dHPC showed a trend for a reduction in dendritic spine numbers (P=0.099), and elevated Gria1 levels (P=0.059).
Conclusions: These findings show that NOS1AP overexpression in dHPC (and partially mPFC) induces schizophrenia related behavioral and morphological phenotypes. This provides important insights into the functional role of nNOS-NOS1AP interaction in schizophrenia, which will be further corroborated by ongoing electrophysiological and morphological investigations. Eventually, our results may guide towards novel and innovative treatment opportunities for schizophrenia.
Supported By: DFG; BMBF
Keywords: Nitric Oxide, AMPA, Schizophrenia, Animal Behavior, Plasticity

F194. Advanced Diffusion Weighted Imaging in a Disc1 Genetic Model of Schizophrenia

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Background: Schizophrenia is a debilitating mental illness affecting perception, cognition, and behavior. DISC1 is a genetic variant of large effect in schizophrenia, influencing neuronal migration and patterning as well as corticogenesis in vivo. We utilized a biallelic CRISPR/Cas9 Disc1 rat knockout model to investigate the contribution of Disc1 to neural microstructure.
Methods: Ex-vivo high-resolution MR imaging of Disc1(-/-) and wild-type age- and sex-matched rats was performed and tract-based spatial statistics (TBSS) for diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) were performed.
Results: TBSS analysis revealed widespread perturbations in white matter structure and organization across all scalar measures of the diffusion tensor in Disc1(-/-) rats most pronounced in neocortex, corpus callosum, and cerebellum. This analysis also revealed voxel-wise changes in parametric measures of orientation and dispersion in neocortex, corpus callosum, and cerebellum.
Conclusions: DTI and NODDI demonstrate the gene-specific contribution of Disc1 to global microstructural alterations. NODDI complements DTI by uncovering novel and previously occult regions of structural change and speaks to the utility of multi-shell diffusion studies in models of neuropsychiatric disease. These findings establish a platform for further exploration into molecular, behavioral, and neuroimaging features of this genetic model.
Supported By: NIH T32 GM007507
Keywords: DISC1, Animal Models, Diffusion Tensor Imaging (DTI), NODDI, Schizophrenia

F195. Evaluation of Translocator Protein Signals and Stress Cascades in Preclinical Models of Psychosis With Inflammatory Disturbances

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Background: Translocator protein 18 kDa (TSPO) has been used to assess neuroinflammatory processes in psychotic disorders. However, it remains unclear whether TSPO can be interpreted as a biomarker for inflammation. Thus, we evaluated the validity of TSPO as a biomarker of inflammation in two mouse models for psychosis with inflammatory disturbances: the maternal immune activation (MIA) and cuprizone short-term exposure (CSE) models. We recently reported that TSPO binding was significantly downregulated in the MIA model. To compare changes in TSPO binding between two models, TSPO autoradiography in the CSE model was conducted. Possible changes in the hypothalamic-pituitary-adrenal axis and oxidative stress in both models were also examined.
Methods: In the MIA model, pregnant C57BL/6J mice were administered polyinosinic:polycytidylic acid (20 mg/kg, i.p.) on embryonic day 9.5. In the CSE model, 8-week-old C57BL/6J mice were fed a diet containing 0.2% cuprizone, a copper chelator, for one week. Ex vivo autoradiography for TSPO was conducted using [125I]iodo-DPA-713. The levels of corticosterone in serum and protein carbonylation in the prefrontal cortex were determined.

Results: TSPO binding was augmented in the CSE model. The levels of serum corticosterone in both MIA ($p=0.005$) and CSE ($p=0.038$) mice were significantly elevated. Decreased protein carbonylation was observed in the MIA ($p=0.0118$), but not CSE mice ($p=0.6228$).
Conclusions: The MIA and CSE models showed difference in TSPO signaling. Stress pathways that are functionally interconnected with the inflammatory responses showed similarities and differences. More careful studies of TSPO distribution in neuroinflammation and other stress cascades will elucidate the biological mechanisms underlying psychosis-related behaviors.
Supported By: K99MH-094408; DA-040127; NARSAD; JST PRESTO JPMJPR14M6
Keywords: Cuprizone Short-Term Exposure (CSE), Maternal Immune Activation, Inflammatory Disturbances, Translocator Protein (TSPO), Psychosis Phenotype

F196. Transgenic Overexpression of the Type III Isoform of Neuregulin 1 in Mice Induces Abnormalities on Auditory Event Related EEG Biomarkers Related to Schizophrenia Accompanied by Reduction of Parvalbumin Positive Interneurons in the Prefrontal Cortex

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Background: Genetic findings in human patients as well as preclinical studies in transgenic mice implicate neuregulin 1 (NRG1) as a critical component in the pathophysiology of schizophrenia. Its predominant neuronal receptor, ErbB4, is primarily expressed in fast-spiking interneurons enabling the maintenance of normal excitatory/inhibitory balance (E/I balance) which can be accessed via electroencephalography (EEG). Patients with schizophrenia show deficits in auditory event-related potentials (AERP), mismatch negativity (MMN) and the 40 Hz auditory steady-state response (ASSR) as well as increased basal gamma oscillation. The NRG1 HapICE risk allele is associated with increased cerebral expression of the NRG1 type III isoform in patients with schizophrenia.
Methods: In the present study, the potential disruption of the E/I balance in transgenic NRG1 type III overexpressing mice (HANI mice) has been investigated by immunohistology for parvalbumin-positive interneurons (PV+IN) in the prefrontal cortex and EEG recordings.
Results: Overexpression of NRG1 type III reduced the number of PV+IN in the prefrontal cortex, abolished MMN, increased the amplitude of AERP, increased basal gamma oscillation and reduced phase-lock coherence in the 40 Hz ASSR compared to wildtype littermates.
Conclusions: In this study, we showed for the first time that overexpression of NRG1 type III leads to a loss of prefrontal PV+IN and deficits in event-related EEG biomarkers, supporting the notion that the NRG1-ErbB4 pathway is involved in maintaining the E/I balance, sensory stimulus processing and ultimately cognitive functions. Our results indicate that the NRG1 type III transgenic mouse model represents a tool with high translational potential to investigate pathological mechanisms related to schizophrenia.
Keywords: Animal Model, Electroencephalography (EEG), Schizophrenia, Parvalbumin Interneurons, E/I Balance

F197. Aripiprazole Lauroxil NanoCrystal® Dispersion: A Potential 1-Day Initiation Regimen for Long-Acting Aripiprazole Lauroxil

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Background: Aripiprazole lauroxil (AL), a long-acting injectable antipsychotic for the treatment of schizophrenia, currently requires 21 days of oral aripiprazole upon initiation. We report results from a phase 1 study investigating a NanoCrystal® dispersion formulation of AL (ALNCD) designed to enable rapid achievement of therapeutic levels of aripiprazole as a potential 1-day regimen.
Methods: This was a pharmacokinetic, safety, and tolerability study to assess 2 initiation regimens plus a dose of AL. The 1-day regimen (a single injection of ALNCD + single 30mg dose of oral aripiprazole) was hypothesized to achieve aripiprazole concentrations comparable with the 21-day regimen (15mg/day oral aripiprazole). Patients were randomized 1:1:1:1 to the 1-day regimen or the 21-day regimen, plus a dose of AL 441 or 882mg.
Results: In total, 133/161 patients completed the study. The 1-day regimen groups had comparable aripiprazole exposure to the corresponding 21-day regimen group. The most common adverse events ($\geq$5.0%) were injection-site pain, headache, increased weight, insomnia, dyspepsia, and anxiety. In total, 4 akathisia events ($n=4$ patients) and 5 akathisia events ($n=2$ patients) occurred in the 1-day and 21-day groups, respectively.
Conclusions: The combination of ALNCD and 30mg oral aripiprazole (as part of a 1-day regimen with AL) is a well-tolerated, adequate substitute for 21 days of oral aripiprazole. Therefore, the 1-day regimen may offer an alternative AL starting regimen that assures therapeutic levels of antipsychotic coverage throughout the initial 21 days of treatment. The ALNCD 1-day regimen is under review by the FDA.

NanoCrystal® is a registered trademark of Alkermes Pharma Ireland Limited.
Supported By: Alkermes
Keywords: Schizophrenia, Aripiprazole Lauroxil, Aripiprazole, Aripiprazole Nanocrystal Dispersion Formulation

F198. Parahippocampal Thickness Predicts Treatment Improvement in Early and Chronic Schizophrenia

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Background: Despite recent advances, there is still a major need for prediction of treatment success in schizophrenia. Cortical thickness measures are relatively easy to obtain and may provide biomarker candidates. Here, we tested a set of candidate brain regions as predictors of treatment response in first episode schizophrenia and in two independent schizophrenia cohorts. Regions included the precuneus, inferior parietal gyrus, superior temporal gyrus, parahippocampal gyrus, anterior cingulate, inferior frontal gyrus, insula, lateral and medial orbitofrontal cortex, and occipital cortex.
Methods: In the discovery cohort, we used the whole sample of patients to estimate individual response slopes using Empirical Bayes, 36 of which had cortical thickness measurements at baseline. Patients were scanned aprior to treatment with either risperidone or aripiprazole. Symptoms were assessed with the Brief Psychiatric Rating Scale at baseline and over the course of up to 52 weeks. Cortical thickness in regions of interest were examined via magnetic resonance imaging and used as predictors of individual treatment response, defined as individual response slope.
Results: Parahippocampal thickness at baseline predicted the individual response to treatment ($P < 0.05$, Bonferroni-corrected). This was replicated in two independent schizophrenia cohorts including a recent onset cohort ($N = 33$) and a sample of chronic schizophrenia patients ($N = 52$), respectively. The overall effect was quantified with an internal meta-analysis ($\beta = 0.4$, 95% CI [0.24; 0.56]; $z = 4.84$, $P < 0.001$).
Conclusions: Parahippocampal thickness may be a promising marker of treatment success both at the early and the chronic stage of schizophrenia.
Supported By: Supported by NIMH grant P50MH080173 to Dr. Malhotra, grant P30MH090590 to Dr. Kane, grant R01MH060004 to Dr. Robinson, grant R01MH076995 to Dr. Szeszko and R21MH101746 to Drs. Robinson and Szeszko.
Keywords: Schizophrenia Spectrum, Prediction of Treatment Outcome, Empirical Bayes, Parahippocampal Gyrus, Cortical Thickness

F199. Comparison of Paliperidone Palmitate 1-Month Vs 3-Month Long-Acting Injectables for Negative Symptom Improvement

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Background: Negative symptoms of schizophrenia are key predictors of long-term disability. This post hoc analysis compared improvement in negative symptoms in patients on paliperidone palmitate 3-month (PP3M) and PP 1-month formulation.
Methods: Data from randomized double-blind (DB), phase-3 study in patients with schizophrenia (DSM-IV-TR) were analyzed. After screening (3 wks), patients entered 17-wk open-label (OL) phase to receive flexible dose PP1M and 48-wk DB phase to receive PP1M or PP3M. Positive and Negative Syndrome Scale scores (PANSS) for PP1M vs PP3M were assessed.
Results: Of 1429 enrolled, 1016 randomized to receive PP3M (n=504) or PP1M (n=512). Mean (SD) age was 38.4 (11.86) yrs. At baseline, the mean (SE) negative subscale total was 23.2 (0.12), indicating moderate-to-severe negative symptoms. Negative subscale and symptoms factor scores showed continuous improvements throughout OL and DB phases - mean (SD) at OL baseline and DB endpoint for total negative subscale score and symptom factor score were 23.2 (4.60) and 22.3 (4.87), and 15.9 (4.99) and 14.9 (4.81), both R2:0.16, respectively. Mean (SD) PANSS negative subscale score changes from DB baseline for PP1M vs PP3M were similar over time (mean change from baseline to DB endpoint was -1.4 (3.67), R2:0.06 vs -1.4 (3.63), R2:0.05).
Conclusions: PP3M and PP1M demonstrated consistent and similar efficacy in patients with moderate-to-severe negative symptoms of schizophrenia over observed timepoints, including patients with predominantly negative symptoms. Longer continuous treatment with PP3M showed greater benefit. Treatment with long-acting injectables for longer than a year was associated with greatest improvements in negative symptoms.
Supported By: Janssen Research & Development
Keywords: Negative Symptoms, Paliperidone Palmitate 1 Monthly, Paliperidone Palmitate 3 Monthly

F200. Relationships Between Mismatch Negativity and Transdiagnostic Symptoms Across Psychotic Disorders

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Background: Schizophrenia is characterized by deficits in the mismatch negativity (MMN), an early event-related potential (ERP) elicited by expectation violations. Deficits in MMN are hypothesized to reflect dysfunction in predictive coding mechanisms implicated in psychotic and disorganized symptoms. Using a dimensional framework, we investigated whether MMN relates to symptoms transdiagnostically across schizophrenia spectrum disorders (SZD), mood disorders with psychosis (MPD) and other psychotic disorders (OPD).
Methods: ERP data were obtained in response to deviant auditory stimuli from a large sample of individuals diagnosed with SZD (N=113), MPD (N=74), OPD (N=24), as well as no psychotic disorders (NPD; N=247). MMN was computed as the amplitude difference between deviant (frequency, duration) and standard auditory stimuli.
Results: Overall effects were examined using ANOVAs. Compared to NPD, individuals diagnosed with psychotic disorders showed significantly smaller MMN amplitudes to deviant stimuli. Among disorders, MMN amplitudes were smallest in SZD, followed by OPD and MPD; however, differences between clinical groups were not significant. Relationships with symptoms were tested using multiple regression: in the psychosis group, reduced MMN was

associated with more severe disorganized symptoms and worse occupational functioning, irrespective of diagnostic groups. Furthermore, there was no interaction between MMN and diagnosis in explaining disorganized symptom or functioning interactions, which provided evidence that these links are transdiagnostic.
Conclusions: This study replicates findings of reduced MMN in schizophrenia within a large, well-characterized psychotic disorder sample. Importantly, these data show that MMN abnormalities are transdiagnostic neural markers of worse disorganized symptoms and occupational functioning in psychosis.
Supported By: MH44801; MH094398;
Keywords: Schizophrenia, ERP, MMN, Transdiagnostic, Psychotic Disorders

F201. Early Sensory Processing Event-Related Potentials Across a Longitudinal Study of First Episode Psychosis

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Background: Evidence suggests early sensory processing is impaired in first episode psychosis (FEP) patients, measured in sensory gating (P50) and mismatch negativity (MMN) event-related potentials (ERPs). However, studies of the longitudinal course of these deficits are rare, so much less is known about the changes over time across the early course of the disease. This study aims to 1) examine P50 and MMN changes between baseline, 12-month, and 24-month follow-ups in FEP patients, and 2) investigate the association of ERPs with functional and clinical measures.
Methods: P50 and MMN ERPs were recorded in FEP patients (n=41) and healthy controls (n=141). Patients were tested across two years and analyzed at baseline (n=36), 12-month (n=17), and 24-month (n=11) timepoints using repeated-measure ANOVAs and regression models.
Results: Impairment of P50 ($F(1,176)=4.03$, $P=0.046$) and MMN amplitude at T8 ($F(1,87)=4.79$, $P=0.03$) in FEP patients was stable over time. A significant time and group interaction in MMN difference (T7-T8 amplitude) was observed ($F(2,109)=4.82$, $P=0.01$) where MMN difference was greater at 24 months compared to baseline ($t(15)=-3.43$, $P=0.01$). Significant relationships were observed between P50 at 12 months and Global Assessment of Functioning (GAF) scores at baseline and between neuroticism personality trait and MMN T7 amplitude at 12 months.
Conclusions: We found deficits of P50 and MMN amplitude at T8 were stable in FEP patients across the first two years of the disease. A MMN lateralization effect was greater in FEP patients over time. Furthermore, baseline GAF predicted sensory gating at 12 months and neuroticism predicted MMN T7 amplitude at 12 months.
Supported By: R01 MH109687
Keywords: First Episode Psychosis, Event-related Potentials, Endophenotypes, Schizophrenia, Bipolar Disorders

F202. Atypical P300 Amplitude Differentiates Conversion Patterns in Psychosis Prodrome When Autism Spectrum Disorder is Comorbid

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Background: Autism spectrum disorder (ASD) and schizophrenia are considered distinct disorders, with ASD characterized by social communication deficits and repetitive behaviors, and schizophrenia by hallucinations and delusions. However, atypical sensory and attentional processing characterizes both disorders, and psychosis symptoms exist disproportionally in ASD. Electrophysiological markers that characterize schizophrenia, including P300 amplitude reductions, are present in individuals at clinical high-risk (CHR) for psychosis. Whether these markers are: present in ASD individuals showing CHR profiles and/or predictive of conversion is unknown. We investigated P300 response and its sensitivity to psychosis conversion across CHR groups with (CHR/ASD+) and without (CHR/ASD−) comorbid ASD.
Methods: Electrophysiological data of 305 CHR patients (14 CHR/ASD+; 291 CHR/ASD−) from the NAPLS-2 Consortium were analyzed. We examined P300 amplitude to infrequent Target (10%) and Novel distractor (10%) stimuli from separate visual and auditory oddball tasks.
Results: P300 amplitude to Novel visual distractor stimuli was smaller in CHR/ASD− converters (n=71) than CHR/ASD− non-converters (n=220), but larger in CHR/ASD+ converters (n=4) than CHR/ASD+ non-converters (n=10) (Modality×ASD×Converter Interaction, $F=3.57$; $p=.06$). For both auditory and visual Target stimuli, whereas P300 amplitude was similar for CHR/ASD+ non-converters and all CHR/ASD− individuals, CHR/ASD+ converters had substantially larger P300 amplitudes (ASD×Converter interaction, $F=12.12$; $p=.001$).
Conclusions: Results revealed dissociable P300 amplitude profiles to visual and auditory target and novel stimuli in CHR patients that differentially predicted subsequent conversion to psychosis, depending on ASD status. Findings suggest CHR patients with ASD might have distinct pathophysiological mechanisms underlying their psychosis risk, requiring separate consideration of both risk biomarkers and intervention strategies.

Supported By: NIMH U01, Seaver Foundation
Keywords: EEG, Autism Spectrum Disorder, Prodromal Psychosis, P300, Oddball

F203. Differential Cognitive Deficits of Two Negative Symptom Domains in Schizophrenia

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Background: Factor analyses of PANSS negative symptoms have identified two factors: expressive and experiential deficits. This study examines the clinical and cognitive correlates of these two factors in schizophrenia patients undergoing Cognitive Remediation.
Methods: One hundred fifty-one subjects age 18 - 55 with schizophrenia or schizoaffective disorder enrolled in a 12-week computerized cognitive remediation study were assessed for demographics, psychopathology (PANSS), cognition (MCBB), and daily living skills (UPSA-Brief). Exploratory (EFA) and confirmatory (CFA) factor analyses of PANSS items, and Pearson's correlations between factors, demographics, MCCB, and UPSA-Brief scores were examined at baseline.
Results: The PANSS Negative Symptom Factor (N1, N2, N3, N4, N6, G7, G16) was analyzed by CFA and revealed a two-factor model: Expressive (N1, N3, N6, G7) and Experiential (N2, N4, and G16) Deficit Factors. There were significant correlations between the Expressive Deficit factor score and cognition: Trail Making Test- A (r=-0.259, t=0.001), BACS Symbol coding (r=-0.287, t=0.001), Category Fluency (r=-0.342, p=0.001), Hopkins Verbal Learning Test – revised (HTLV-R) (r=-0.236, p=0.05), Letter Number Sequencing (r=-0.256, P=0.001), and NAB Mazes (r=-0.409, p=0.001). The Expressive Deficit factor was significantly correlated with Processing Speed (r=-0.352, p=0.001) and Reasoning/Problem Solving (r=-0.338, p=0.001) domains. There were no significant correlations between either factor and UPSA-Brief or the MCCB cognitive composite score.
Conclusions: Our results support the negative symptom two-factor model of Expressive Deficit and Experiential Deficit domains. Only the Expressive Deficit factor was associated with baseline cognitive deficits suggesting a more profound neurobiological dysfunction underlying this factor.
Keywords: Negative Symptoms, Cognitive Deficits, Schizophrenia, Schizoaffective Disorder, Factor Analysis

F204. Complex Mismatch Negativity is Reduced in the First Episode Schizophrenia-Spectrum on an Ascending Pitch Pattern Task

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Background: Mismatch negativity (MMN) is an event-related potential elicited by deviant auditory stimuli. The MMN to simple physical changes (simple mismatch: sMMN) such as pitch or duration is drastically reduced in chronic schizophrenia participants (Sz), but not in first-episode schizophrenia patients (FESz). MMN can also be elicited by deviant stimuli that violate a more complex pattern rule. Complex pattern MMN (complex mismatch: cMMN) was examined to a stimulus that violated an ascending pattern in FESz patients to determine if cMMN was impaired in the context of intact sMMN.
Methods: Thirteen FESz and 12 HC watched a silent film while groups of 3 tones were presented. The standard sequence ascended in pitch (50 ms, 330 ms SOA, 90%). The last tone of deviant group (10%) descended in pitch, violating the ascending pattern. Groups were separated by 1000 ms. cMMN was visualized by subtracting the "standard" ending tone waveform from the "deviant" ending tone waveform.
Results: Analyses of the late cMMN revealed significant reductions in FESz (p=.014). The effect size for the reduction was d =1.05. This was contrasted with a sMMN deficit of d =0.2 or less.
Conclusions: Preliminary results indicate that cMMN is reduced among FESz with a large effect size within the context of normal sMMN. cMMN could potentially serve as a biomarker of disease presence prior to the onset of psychosis; whereas sMMN appears to be a biomarker of disease progression, cMMN may help determine risk for transition to psychosis among clinical high risk individuals.
Supported By: NIH RO1 MH94328
Keywords: Mismatch Negativity, First Episode Psychosis, Biomarkers

F205. Mismatch Negativity Correlates With Auditory Cortex Gray Matter and Prodromal Role Functioning in First Episode Schizophrenia Spectrum Individuals

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Background: Primary auditory cortex gray matter in Heschl's gyrus (HG) is reduced and correlated in the left hemisphere with pitch-deviant mismatch negativity (pMMN) in first hospitalized schizophrenia. Correlations between pMMN and duration-deviant mismatch negativity (dMMN) amplitude and HG, and MMN and HG impact on pre-psychosis role functioning were examined in first episode schizophrenia-spectrum subjects at first psychiatric contact (FESz).
Methods: Forty FESz and 40 matched (age, sex, IQ, pSES) healthy controls (HC) were tested. For MMN, pitch deviant (1.2 kHz, 50 ms, 10%) and duration deviant (100 ms, 10%) tones were interspersed among standard tones (1 kHz, 50 ms, 330 ms SOA). pMMN and dMMN were measured at Fz. Role functioning was measured with the Cornblatt Global Functioning: Role scale. Twenty-eight FESz and 28 HC underwent

structural MRI. Left and right HG were manually edited and measured using Freesurfer.
Results: Smaller MMN reflected worse role functioning prior to hospitalization (pMMN: rho= -.35, p =.03, dMMN: rho= -.41, p <.01). Less left (but not right) HG gray matter was associated with smaller pMMN (rho= -.40, p =.03) and dMMN (rho= -.47, p .01). Role functioning and HG were not correlated. There were no significant correlations in HC.
Conclusions: pMMN and dMMN are suitable biomarkers of disease progression as reflected in reduced left HG. Presumably, poorer role functioning and less gray matter reflect more of the pre-psychosis progressive pathological process in the prodrome. pMMN and dMMN may serve as sensitive outcome measures for therapeutic interventions early in psychosis.
Supported By: NIH P50 MH103204, RO1 MH94328
Keywords: First Episode Psychosis, Mismatch Negativity, Heschl's Gyrus, Role Functioning, Biomarkers

F206. Spontaneous Gamma EEG Activity and Aging in Schizophrenia

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Background: Spontaneous gamma (SG; 30-100 Hz) activity has been related to cortical excitation/inhibition balance. We previously reported that SG power was increased in individuals with schizophrenia (SZ) compared to healthy controls (HC) during auditory steady-state stimulation, consistent with evidence of increased cortical excitability in schizophrenia. Increased spontaneous EEG activity has also been reported in healthy aging. As SZ is associated with accelerated neuroanatomical aging, here we investigated whether SG power in SZ increased with age to a greater degree than in HC.
Methods: Subjects were 23 HC and 24 SZ, matched on age (mean 45 years) and other variables. Subjects performed auditory and visual oddball tasks during EEG recording. Following artifact correction, SG power was measured in the pre-stimulus baseline (500 ms) with the Fast Fourier Transform.
Results: Overall, SG power was higher in Old vs Young subjects ($p < .05$) and higher in the Visual than Auditory modalities ($p < .05$), but there was no difference between HC and SZ. In the Auditory modality, SG power was higher in SZ than HC in Young ($p < .01$) but not Old subjects, and SG power increased with age in HC ($p < .001$) but not SZ.
Conclusions: SG power increased with age overall, supporting the hypothesis that spontaneous neural activity increases with age. However, contrary to our hypothesis, we found no effect of aging on SG in SZ. Instead, SG may be decoupled from age-related neuroanatomical changes in schizophrenia. Increased SG power in SZ could reflect an excitation/inhibition imbalance that precedes progressive neuroanatomical changes.
Supported By: NARSAD Independent Investigator Award (KS); Department of Veterans Affairs I01 CX001443 (KS); NIH R01 MH093450 (ML, KS)
Keywords: Schizophrenia, Aging, Electroencephalography (EEG), Gamma Oscillation, E/I Balance

F207. Neurocognition and Adaptive Functioning in the 22q11.2 Deletion Syndrome Model of Schizophrenia

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Background: Identifying factors that influence functional outcome is an important goal in schizophrenia research. The 22q11.2 deletion syndrome (22q11DS) is a unique genetic model with high risk (20-25%) for schizophrenia. This study aimed to identify potentially targetable domains of neurocognitive functioning associated with functional outcome in adults with 22q11DS.
Methods: Principal component analysis using data from a comprehensive battery of 15 neurocognitive tests for 99 adults with 22q11DS (n=43 with schizophrenia) revealed four domains of neurocognition (Verbal memory, Visual memory, Motor functioning, and Executive performance). Subsequently, we investigated the association of these domains with adaptive functioning. We used Vineland Adaptive Behavior Scales (VABS) data available for 84 subjects in a linear regression, accounting for schizophrenia status and overall intellectual level.
Results: The model explained 46.8% of variance in overall functional outcome ($p < 0.0001$) and 47.7% of variance in daily living skills ($p < 0.0001$). VABS adaptive functioning scale scores were higher in those with better performance on Executive domain tests, no psychotic illness, and older age. The effects of Executive Performance on functioning did not significantly differ between those with and without psychotic illness.
Conclusions: The significant relationship between Executive Performance and functional outcome is a novel addition to our understanding of cognitive factors that may contribute to functional outcome in schizophrenia high-risk groups. The results provide impetus for further studies of Executive Performance as a potential target of early intervention strategies to mitigate risk for schizophrenia and functional deterioration.
Keywords: Adaptive Functioning, Neurocognition, Schizophrenia, 22q11DS, High-risk

F208. Patients With Schizophrenia Have Reduced Tendency Towards Model-Based Decision Making, Which is not Linked With Ventral Striatal Presynaptic Dopamine as in Healthy Controls

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Background: Human decision-making ranges between the extremes of model-free (i.e., relying only on previous

outcomes) and model-based (i.e., implementing cognitive models) behavior. Model-based/model-free decision-making can be investigated using sequential decision tasks; studies employing such paradigms suggest a decreased tendency towards model-based behavior in patients with schizophrenia. Furthermore, model-based decision making is associated with dopamine function. In schizophrenia, particularly presynaptic striatal dopamine synthesis is increased. Therefore, we hypothesized that impaired model-based decision-making in schizophrenia is associated with abnormal striatal dopamine synthesis.

Methods: 26 patients with chronic schizophrenia, currently in psychotic remission, and 22 healthy controls (matched by age and gender) were enrolled in the study. Model-based/model-free decision-making was evaluated with a two-stage Markov decision task, followed by computational modeling of subjects' learning behavior, resulting in several parameters including tendency for model-based decisions. Presynaptic dopamine synthesis was assessed by 18F-DOPA positron emission tomography and subsequent graphical Patlak analysis. Associations between decision-making parameters and ventral striatal 18F-DOPA uptake were tested by partial correlation analyses.

Results: Patients with schizophrenia showed a significantly decreased tendency towards model-based decision-making ($p=0.03$). 18F-DOPA uptake in the ventral striatum was increased in patients ($p=0.04$). In healthy controls, ventral striatal 18F-DOPA uptake was positively correlated with the tendency towards model-based behavior ($p=0.006$; controlling for age, gender, and remaining striatal 18F-DOPA uptake), but not in patients ($p=0.69$). Correlation coefficients differed significantly between groups ($p=0.03$).

Conclusions: Results demonstrate a lost association between ventral striatal dopamine synthesis and model-based decision-making in schizophrenia, potentially due to increased presynaptic dopamine function.

Supported By: Studienstiftung des deutschen Volkes; Bundesministerium für Bildung und Forschung; Deutsche Forschungsgemeinschaft; Kommission für Klinische Forschung der Technischen Universität München

Keywords: Decision Making, Model-Based and Model-Free Decisions, Schizophrenia, Dopamine, Striatum

F209. Semantic Processing Abnormalities and Their Relationship to Symptoms in Persons at Clinical High Risk for Schizophrenia: An Event-Related Brain Potential Study

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Background: Persons exhibiting clinical high-risk (CHR) symptoms similar to but milder than those of schizophrenia have an elevated risk of developing this disorder. We sought evidence that CHR patients process relationships between meaningful concepts abnormally, similar to what has been observed in schizophrenia, and that these abnormalities are related to psychosis-like symptoms. To probe how meaningful stimuli activate related concepts in semantic memory, we measured the N400 event-related potential (ERP) response. We hypothesized that the normal reduction in N400 amplitude for stimuli that are more related to a preceding one is decreased in CHR patients, and that this abnormality correlates with psychosis-like symptoms.

Methods: We recorded ERPs in 16 CHR and 16 healthy control participants who viewed prime words followed at either 300- or 750-ms stimulus-onset asynchrony (SOA) by targets which were either words related or unrelated to the prime, or pronounceable nonwords. Participants' task was to indicate whether or not the target was a word. Patients' psychosis-like symptoms were assessed with the Structured Interview for Psychosis-Risk Syndromes.

Results: Consistent with our hypothesis, across SOAs, N400 amplitudes were larger (more negative) for unrelated than related targets in controls, but did not differ between these conditions in patients (Tukey HSD familywise $\alpha<0.05$). Across patients, smaller N400s for unrelated targets at the short SOA correlated with suspiciousness/persecutory ideation (Spearman's $\rho=0.66$, $p=0.008$).

Conclusions: Persons in early stages of the developmental trajectory to psychosis appear to process related and unrelated stimuli more similarly than normal. This abnormality may represent a neurophysiological mechanism of the development of delusions.

Supported By: Ontario Mental Health Foundation; Province of Ontario Academic Health Science Centre AFP Innovation Fund

Keywords: Clinical High-Risk States for Psychosis, Event-related Potentials, Delusions, Semantic Association, Language

F210. The Role of Catecholamines in Information Gathering

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Background: The arbitration between timely choice and extended information gathering is critical for effective decision making. Impaired arbitration has been reported in psychiatric disorders such as schizophrenia and obsessive-compulsive disorder, but little is known about the neurocognitive control mechanisms driving information gathering.

Methods: To understand the role of noradrenaline and dopamine in information gathering, we conducted a double-blind, placebo-controlled, between-subjects drug study. Groups of 20 subjects each received either a noradrenaline beta-receptor antagonist (40mg propranolol), a dopamine D2/3 receptor blocker (400mg amisulpride) or placebo before playing an information sampling task. A Bayesian model was used to investigate the computational processes driving information gathering of each participant.

Results: Noradrenaline blockade led to reduced information gathering, independent of external costs of sampling ($F(2,57)=4.29$, $p=.018$). No significant effect was observed for dopamine blockade ($p>.05$). Computational modelling revealed that noradrenaline modulated the emergence of an urgency signal, which depicts how the subjective costs of sampling increase with time. This urgency escalated significantly earlier in the noradrenaline group (fixed condition: $p=.003$, decreasing condition $p=.029$, cluster-extend corrected using permutation tests).
Conclusions: Our findings show that noradrenaline plays a critical role in this task, which is highly relevant for several psychiatric disorders. Our findings thus indicate that noradrenaline might be an important focus for intervention in patients affected by information-gathering cognitive biases.
Supported By: Wellcome Trust; Jacobs Foundation; Biomedical research council; Gatsby Foundation
Keywords: Noradrenergic System, Decision Making, Computational Modeling, Computational Psychiatry

F211. A Causal Role for Noradrenaline in Balancing Beliefs Against Reality

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Background: Providing a neurocomputational account of how 'top-down' prior expectations are balanced against 'bottom-up' sensory reality is one of the core aims of computational psychiatry, as prediction error processing may be vulnerable in many psychopathologies (e.g. psychosis, autism, anxiety). Here we conducted a computational-pharmacology study to address the role of noradrenaline (NA) in signalling uncertainty during the computation of prediction errors.
Methods: Behavioural effects of the non-selective β-adrenergic receptor antagonist Propranolol (40mg) were probed using a between-subjects, double-blind, placebo-controlled design. Healthy volunteers ($n=21$, Propranolol, $n=19$, Placebo) performed a probabilistic associative learning task. A hierarchical learning model fit to participant behaviour allowed us to formally quantify 'surprise' (prediction errors) about cue-outcome contingencies and changes in these associations over time (volatility). Concurrent pupillometry provided a biomarker of phasic noradrenergic responses.
Results: We observed a significant three-way interaction between expectation, sensory noise, and drug ($P<0.02$). Under placebo, reaction times were slower for unexpected, relative to expected, stimuli when sensory noise was high ($P<0.001$). This effect was enhanced following NA antagonism (i.e. greater RT difference, $P<0.02$) and learning rates were reduced ($P<0.05$). Computational-pupillometry analyses indicate that, while pupil dilation increases with increasing volatility, this is significantly reduced under Propranolol (cluster-based permutation approach at 2000 permutations (FWE alpha=0.05, 2-tailed).
Conclusions: These findings provide direct evidence for noradrenaline's role in shifting the balance between prior beliefs and sensory inputs by signalling the changeability of the environment, and provide a computational framework for understanding how catecholaminergic drugs might treat psychopathologies that involve problems integrating expectations with reality.
Supported By: Wellcome Trust
Keywords: Noradrenaline, Computational Modeling, Computational Psychiatry, Prediction Errors, Propranolol

F212. Convergent and Divergent Validity of the Prodromal Questionnaire Negative Symptom Subscale

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Background: Negative symptoms are associated with risk for psychosis and poorer outcomes. The Prodromal Questionnaire (PQ) is a self-report questionnaire used to screen for prodromal and psychotic symptoms. However, the PQ-negative symptom subscale has not been examined for convergent or divergent validity.
Methods: Young adults ($N=1,556$) completed the PQ, Temporal Experience of Pleasure Scale, and commonly used questionnaires assessing anxiety, depression, and motivation. An EFA was conducted on the PQ-negative symptom items. Difference tests were conducted to investigate whether PQ-negative items, or either of their underlying factors, were more strongly related to valid measures of negative symptoms or to measures of other psychopathology.
Results: The EFA produced a two-factor solution. Results indicated that PQ-negative items were significantly more correlated with measures of depression ($r=.670$, $p<.001$) and anxiety ($r=.598$, $p=<.001$) than with measures of negative symptoms (rs ranged from -.171 to .296; all $ps<.001$; positive correlation with amotivation and negative correlations with autonomous motivation, control motivation, and pleasure subscales). The resultant EFA factors were significantly more correlated with depression (rs ranged from .567 to .672; $ps<.001$) and with anxiety (rs ranged from .493 to .619; $ps<.001$) than with other measures of negative symptoms (rs ranged from -.178 to .220; all $ps<.001$; positive correlation with amotivation and negative correlations with autonomous motivation and pleasure subscales).
Conclusions: The PQ-negative items appear to be more strongly associated with mood and anxiety symptoms than with negative symptoms related to motivation and pleasure, suggesting poor convergent and divergent validity.
Keywords: Psychosis Risk, Anxiety, Depression, Negative Symptoms

F213. Eighteen-Year Course of Cognitive Functioning in Psychotic Disorders

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Background: Knowledge is limited regarding the long-term course of cognitive functioning in individuals with psychotic

disorders. We thus investigated cognitive functioning at 2- and 20-years follow-up in an epidemiological cohort of first admissions with psychotic disorders.

Methods: Data came from the prospective Suffolk County Mental Health Project (SCMHP). Cognitive tests were administered 2-years (n = 399; schizophrenia spectrum: 189, affective psychoses: 148, other psychoses: 62) and 20-years (n = 241; 115, 92, and 34, respectively) after baseline assessment. A comparison group having no history of psychosis (n = 260) was assessed at year 20.

Results: Individuals with schizophrenia spectrum disorders showed poorer cognitive functioning overall than those with affective and other psychoses. SCMHP participants declined on most tests (d = 0.24 (range 0.12- 0.44)), with comparable slopes across diagnoses. Longer duration of untreated psychosis and low premorbid IQ were significantly associated with clinically relevant declines (>0.5 SD) in vocabulary and processing speed but not in other areas. Cross-sectional comparisons showed that compared to controls, the SCMHP cohort with psychosis functioned more poorly and showed greater age-specific impairments in vocabulary knowledge, verbal fluency, and abstraction-executive functioning after age 40.

Conclusions: Cognitive decline is neither specific to nor more pronounced in schizophrenia than in other psychotic disorders. In psychotic disorders, impairments in some key cognitive domains relative to never-psychotic individuals seem to increase from middle age onwards, possibly suggesting premature aging or neuro-degeneration. Our findings stress the potential of cognitive interventions that can reduce and/or slow declines in cognitive function that precede or exceed normal aging.

Supported By: NIH

Keywords: Cognition, Course of Illness, Psychotic Disorders, Longitudinal Study

F214. Health Care Resource Utilization is Higher in Patients Prior to Diagnosis With Schizophrenia Than Non-Schizophrenia Comparators in a Large Commercially Insured Population in the United States

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Background: Schizophrenia is associated with considerable health care resource utilization (HCRU), yet little is known about pre-diagnosis patterns of HCRU in these patients. We examined HCRU of patients with and without schizophrenia over a 5-year pre-diagnosis period.

Methods: This US-based retrospective study used claims data (HealthCore Integrated Research Database) to identify newly diagnosed patients with schizophrenia aged 15–54 years at diagnosis. Patients with schizophrenia were compared with a demographically matched (1:4) non schizophrenia cohort for up to 5 years pre-diagnosis (12-month intervals). All-cause and behavioral health-related HCRU are described.

Results: The schizophrenia and comparator cohorts included 6,732 and 26,928 patients, respectively. The percentage of individuals with ≥1 all-cause inpatient hospitalization in the 0–12 months pre-diagnosis was 32.7% for schizophrenia versus 3.9% for comparators. Patients with schizophrenia had more all-cause physician office visits across all pre-diagnosis intervals versus comparators (schizophrenia, range: 4.5–5.5; comparators, range: 3.1–3.2). Behavioral health-related HCRU was also higher across pre-diagnosis intervals for schizophrenia versus comparators: 1.8–2.9 vs 0.1 psychiatrist visits, 1.0–1.2 vs 0.2 psychologist visits, and 2.1–4.1 vs 0.3 pooled psychiatrist/psychologist visits respectively. Antipsychotic medication claims were also greater for schizophrenia vs comparators (21.8%–56.6% vs 0.7%–1.0% of patients, respectively).

Conclusions: For up to 5 years pre-diagnosis, patients with schizophrenia have higher all-cause and behavioral health-related HCRU and anti-psychotic use versus matched comparators. This study improves understanding of patients who develop schizophrenia; early identification and treatment of patients prior to schizophrenia diagnosis could be optimized and is warranted.

Supported By: Boehringer Ingelheim (ANTHEM)

Keywords: Psychiatry, Schizophrenia, Medical Decision Making, Healthcare Utilization

F215. Gene- and Pathway-Based Analysis of the Ischemia-Hypoxia Response to Developmental Adversities: Testing the Developmental Origins of Health and Disease (DOHaD) Model in Mental Health

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Background: Developmental adversities confer risk for mental disorders in adulthood, but the relation is complex due to substantial heterogeneity driven by differential genetic vulnerability. By applying gene- and pathway-based analyses for genes involved in a biologically relevant putative mechanism for pre- and perinatal adversities—the ischemia–hypoxia response (IHR)—, we tested their role as a function of developmental adversities in the risk for mental ill-health.

Methods: First, in a female twin cohort(n=334), main and interacting effects of a priori selected candidate SNPs on the basis of our prior systematic identification of genes associated with both IHR and schizophrenia and prospectively collected obstetric complications (OC) on mental ill-health were investigated. Second, in a large case-control sample (EU-GEI), a

polygenic risk score (PRS) of IHR pathway (constructed based on pre-registered gene-set) was generated by cross-referencing PGC2 data.
Results: In the first sample, SNPs in AKT1, BDNF, CHRNA7, GABRB2, PLXNA2, RELN, RGS4, and YWHAE moderated the associations between OC and mental ill-health including psychosis expression, while only AKT1 showed evidence for an interaction in gene-based analytical approach($p=0.01$). In the second sample, the case-control analyses revealed that PRS for IHR was associated with schizophrenia($p<0.1E-05$).
Conclusions: Our findings showing main and interacting effects of the IHR with OC provide support for the developmental origins of mental ill-health. To execute the next steps of biologically informative gene-environment approach (IHR and OC), we will leverage an independent population-based twin cohort ($n=704$) with deep-phenotyping, GWA data, methylation profile, in which we demonstrated a main effect of OC on mental ill-health and psychosis expression ($p=0.01$).
Supported By: The European Community's Seventh Framework Program under grant agreement No. HEALTH-F2-2009-241909 (Project EU-GEI); The East Flanders Prospective Twin Survey (EFPTS).
Keywords: Fetal Origins, Gene x Environment, Schizophrenia, Obstetric Complications, Genome-Wide Gene-Environment Interaction Study

F216. Genotype and Early Life Stress Interaction on FKBP5 Methylation in Schizophrenia

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Background: Epigenetic modulation of genes involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis has been hypothesized to be a mechanism explaining the association of early life stress and vulnerability to mental illnesses, including schizophrenia. However, there has been little direct evidence of this mechanism in schizophrenia.
Methods: In a sample of 87 patients with schizophrenia and 95 healthy volunteers, we examined levels of methylation at two loci and a functional polymorphism (rs1360780) of FK506 binding protein 5 (FKBP5), a glucocorticoid receptor regulatory gene where these epigenetic and genetic variants have previously been found to mediate the influence of early life stress on later psychopathology.
Results: Results indicate a 3-way interaction between rs1360780 genotype, diagnosis, and early life experience of violence on average methylation of Intron 2 ($F(1,172)=10.06$, $p=.002$). Post-hoc tests show that among patients with the risk allele, those with early life experience of violence showed lower methylation of Intron 2 compared to patients with the risk allele who did not report exposure to violence, patients with exposure to violence who had the protective allele, and controls with exposure to violence and the risk allele. Additionally, among patients there was a genotype x early life stress interaction on BPRS psychosis subscale scores ($F(1,90)=8.66$, $p=.004$), with patients with a risk allele and exposure to violence having higher BPRS scores.
Conclusions: These results indicate that the epigenetic modulation of FKBP5 by early life stress previously established as a risk factor for depression and PTSD may also contribute to risk of schizophrenia, and positive psychotic symptoms in particular.
Supported By: K23MH112010
Keywords: Epigenetics, Schizophrenia, Childhood Trauma, FKBP5, Gene x Environment

F217. Genome-Wide Analyses of Smoking Behaviors in Schizophrenia: Findings From the Psychiatric Genomics Consortium

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Background: Currently, 17% of US adults and upwards of 60% of those with schizophrenia (SCZ) spectrum disorders smoke tobacco regularly, and several lines of evidence support a shared etiological basis. Notably, the nicotinic acetylcholine receptor gene cluster that has been shown to influence heaviness of smoking in the general population was also reported as one of the 108 SCZ-risk loci identified in the Psychiatric Genomics Consortium (PGC) study of SCZ.
Methods: We investigated the genetic relationship between SCZ and smoking using polygenic risk scores constructed from results from the Tobacco and Genetics (TAG) meta-analyses of genome-wide association studies (GWAS) of smoking behaviors. The availability of smoking data in the PGC-SCZ facilitated analyses of smoking initiation (SI) and cigarettes-per-day (CPD), including association with TAG-based polygenic scores, and exploratory SCZ case-only GWAS.
Results: Polygenic scores based on TAG results for SI significantly predicted SCZ case status in the full PGC cohort ($R2=0.0015$, $P=8.11\times10\text{-}15$), as did scores based on results for CPD ($R2=0.0005$, $P=4.18\times10\text{-}6$). These scores also significantly predicted SI ($R2=0.0047$, $P=6.29\times10\text{-}5$) and CPD ($R2=0.0007$, $P=0.0067$), respectively, among SCZ patients. In the replication phase of the cases-only GWAS of CPD, we identified a genome-wide significant association upstream of TMEM106B on chromosome 7 (rs148253479; $P=3.18\times10\text{-}8$).
Conclusions: We provide evidence of a partially shared genetic basis for SCZ and smoking behaviors. Preliminary case-only results highlight novel SCZ specific genetic liability for smoking quantity. Future research needs to address mechanisms underlying associations between these traits to aid both SCZ and smoking treatment and prevention efforts.
Supported By: The work specific to this report was funded by the United States Department of Veterans Affairs Merit Review Program (5I01CX000278) to Ayman H. Fanous.
Keywords: Schizophrenia, Tobacco, GWAS, Genetic Association, Genetic Correlation

F218. Interaction of Recent Stressful Events and 108 Schizophrenia Risk Loci in Predicting Emergent Suicidal Ideation in Schizophrenia

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Background: Suicide accounts for 5% of deaths in schizophrenia. Recently, 108 genetic risk loci conferring a polygenic risk score for schizophrenia were validated. The risk score was associated with suicidal ideation, a precursor to completed suicide triggered by recent stressful events. However, the interaction between stressful events and the risk loci remains unknown. Thus, we investigated this interaction in conferring risk for emergent suicidal ideation.
Methods: Participants were assessed at baseline and 3-month follow-up. Stressful events were assessed at 3-month follow-up using the Social Readjustment Rating Scale (SRRS). Blood was collected for analyzing the 108 risk loci. Suicidal ideation was assessed at baseline and 3-month follow-up using the Columbia-Suicide Severity Rating Scale. Presence or absence of emergent suicidal ideation at 3-month follow-up was determined, comparing baseline with 3-month assessment.

Logistic regression analyses were done to determine the ability of the 3-month SRRS total score and specific stressful event subcategory scores to predict emergent suicidal ideation. Similar analyses were done for the predictive ability of the individual risk loci, polygenic risk scores, and individual risk loci-stressful event interaction and polygenic risk score-stressful event interaction.
Results: Preliminary analysis (n=95) revealed that higher SRRS total scores (p=0.003), and specifically, medical problems (p=0.002; OR=2.646; 95%CI=1.445-4.846) increased risk for emergent suicidal ideation. Analysis of 106 loci (n=16) revealed risk variant markers rs950169 (OR=8.857, 95% CI=0.7669-102.3) and rs6670165 (OR=7.247, 95% CI=0.7263-72.31) increased risk for emergent suicidal ideation ($p<0.1$). Preliminary interaction analyses were not significant.
Conclusions: Stress and genetics interaction analyses can improve our understanding of the complex pathways leading to suicide.
Supported By: CIHR, AFSP, University of Toronto
Keywords: Suicidal Ideation, Schizophrenia, Stressful Events, Risk Loci

F219. Brain Metabolites and the Relation With Cognition and Psychotic Symptoms in Medication-Free Psychosis and Controls: A Pharmacological Magnetic Resonance Spectroscopy Study

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Background: Several neurotransmitters and neurometabolites have been related to psychotic disorders. One neurotransmitter system increasingly associated with psychosis is the cholinergic muscarinic system. The present study investigated brain metabolite concentrations, their responsivity to M1 receptor blockage, and their relation to cognitive and psychotic symptoms in psychosis.
Methods: 31 medication-free subjects with a psychotic disorder (mean age 27 years) and 31 matched control subjects (mean age 25 years) were enrolled in the study. 1H-proton magnetic resonance spectroscopy (1H-MRS) was used to measure brain metabolites (choline, glutamate, glutamine, GLX, myoinositol, N-acetylaspartate and gluthatione (ratio to creatine)) in the anterior cingulate cortex (ACC) and striatum. Metabolite concentrations, cognitive functioning and psychotic symptom severity were measured both after placebo and after a M1 receptor antagonist (4 mg. biperiden).
Results: After placebo, ACC and striatal metabolite levels did not differ between the psychosis and control group. M1 blockade did not affect brain metabolite levels in these regions and no interaction effects were found. In both groups, metabolite concentrations were not correlated with cognitive functioning. In the psychosis group, a positive correlation was found between striatal choline levels and negative symptom severity (p=0.024).
Conclusions: These results suggest that there are no differences in ACC and striatal brain metabolites between medication-free subjects with a psychotic disorder and controls and that these metabolites are not influences by acute muscarinic M1 receptor antagonism. The correlation between striatal choline and negative symptom severity in the psychosis group suggests that the cholinergic system is involved in negative symptom pathology.
Supported By: ZonMW
Keywords: Psychotic Disorders, Neurocognition, Magnetic Resonance Spectroscopy, Muscarinic Subtype 1 Receptor, Choline

F220. Aberrant Prefronto-Motor Cortex Connectivity Explains Inhibitory Deficits in the Motor Cortex of Patient With Schizophrenia

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Background: The inhibitory deficits in motor cortex in schizophrenia (SZ) has been well demonstrated using short-interval intracortical inhibition (SICI). However, whether the sources of such inhibitory deficits were at motor cortex (M1) locally or abnormal modulations from other non-motor brain areas is still unclear. Here, we combined SICI, diffusion tensor imaging (DTI) and resting-state fMRI (rsfMRI) to further evaluate whether non-motor brain areas might modulate SICI in SZ.
Methods: SICI, DTI and rsfMRI were obtained from 24 SZ patient and 30 healthy controls (HC). Individual stimulation sites for SICI at the left M1 were used as the seeds to obtain the whole-brain functional connectivity (FC) maps. The severity

of clinical symptoms was represented by Brief Psychiatric Rating Scale (BPRS) score. The FC clusters showed significant associations with both SICI and BPRS were further correlated with underlying white matter microstructures.

Results: For SZ group, left prefronto-M1 FC was associated with both SICI ($r=-0.69$, $p=0.0002$) and BPRS ($r=-0.77$, $p<0.0001$); it was also positively correlated with the underlying white matter–left corona radiata(CR), which is the structure connecting ipsilateral frontal-motor cortices ($r=0.54$, $p=0.006$). However, no such correlation was observed in HC group (SICI: $r=0.02$, $p=0.90$; left CR: $r=0.13$, $p=0.50$).

Conclusions: For SZ patients, stronger left prefronto-M1 connectivity, accompanied by better left CR integrity, predicts less severe symptoms and less inhibitory deficits in M1, suggesting the inhibitory deficits in M1 in schizophrenia are partially modulated by remote prefrontal areas.

Supported By: R01MH085646; U01MH108148; P50MH103222; T32MH067533; NARSAD

Keywords: Schizophrenia, SICI, Resting, Functional Connectivity, TMS

F221. Brain Abnormalities and Cognitive Deficits in First-Degree Relatives of Patients With Schizophrenia

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Background: Structural brain abnormalities and cognitive deficits have been reported in first-degree relatives of patients with schizophrenia, suggesting that the deficits observed in patients may be explained by the familial vulnerability for the disease. Here we investigated whether brain abnormalities in non-psychotic relatives differ per type of first-degree relative, whether brain abnormalities scale with the relative risk to develop the illness in different relative types, and how these findings are related to cognitive functioning.

Methods: A total of 980 individuals from five schizophrenia family cohorts [20 MZ co-twins, 25 DZ co-twins, 40 offspring, 201 siblings, 44 parents, 432 controls, and 218 patients] were included. We compared brain measures between each type of relative, and the relatives combined as a group, with the control subjects. Analyses were performed without and with correction for IQ, to investigate the possibly mediating role of cognitive deficits.

Results: As a group, relatives had significantly smaller intracranial, surface area, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, thalamus, putamen, amygdala and accumbens volumes as compared with controls (Cohens d's<-0.19). When comparing the different relative types, the offspring showed the largest effect sizes. After correction for IQ most of the effects in the relatives disappeared, except for smaller cerebellar white matter volume ($d=-0.20$).

Conclusions: These findings suggest that there is a genetic vulnerability that predisposes for smaller brain volumes and lower IQ in families at risk for schizophrenia, but additional environment-by-gene interactions will eventually give rise to the disorder.

Keywords: Schizophrenia, IQ, First-Degree Relatives, sMRI

F222. Temporoparietal Junction Functional Connectivity in Early Schizophrenia and Major Depressive Disorder

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Background: The temporoparietal junction (TPJ) has been linked to lower-level attentional and higher-level social processing. We examined resting functional connectivity of bilateral anterior and posterior TPJ in schizophrenic (SZ) and major depressive disorder (MDD) patients.

Methods: Resting-state fMRI data were acquired from 24 SZ, 24 MDD, and 24 age-matched controls. We performed seed-based connectivity analyses with seeds in bilateral anterior and posterior TPJ, covarying for gender and smoking ($p < 0.05$, FWE-corrected; SPM8).

Results: SZ had reduced connectivity versus controls between left anterior TPJ and dorsolateral prefrontal cortex (dlPFC) and posterior cingulate cortex (PCC), between left posterior TPJ and middle cingulate, left dorsal PFC, and right lateral PFC, between right anterior TPJ and bilateral PCC, and between right posterior TPJ and middle cingulate, left posterior insula, and right insula. MDD had reduced connectivity versus controls between left posterior TPJ and right dlPFC, and between right posterior TPJ and PCC and dlPFC. Lastly, we found reduced connectivity in SZ versus MDD between right posterior TPJ and left fusiform gyrus and right superior-posterior temporal cortex.

Conclusions: This is the first study to measure the functional connectivity to bilateral anterior and posterior TPJ in both SZ and MDD. We observed deficit connectivity between directed effort regions and all four sub-regions of the TPJ in the SZ group versus controls, and only between the right posterior TPJ and one directed effort region in the MDD group versus controls. We detected reduced connectivity in SZ versus MDD between right posterior TPJ and posterior brain regions.

Supported By: CIHR

Keywords: Schizophrenia, Major Depressive Disorder (MDD), Temporo-Parietal Junction, Resting State Functional Connectivity

F223. Withdrawn

F224. Thalamic Dysconnectivity in the Psychosis Risk Syndrome and Early Illness Schizophrenia

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Background: Schizophrenia has been associated with thalamic hyperconnectivity with sensory regions and hypoconnectivity with cerebellar and prefrontal regions. While this pattern has been consistently replicated in chronic schizophrenia samples, less is known about when these abnormalities emerge in the illness course and if they are present prior to illness onset.
Methods: Resting-state fMRI data were collected from clinical high-risk youth (n = 45; CHR), early illness schizophrenia (n = 74; ESZ) patients, and healthy controls (n = 85; HC). Age-adjusted whole-brain functional connectivity, seeded from the thalamus, was compared among the three groups. Main effects of group (FDR-corrected, $p < .01$) were followed up with pairwise comparisons (Tukey-corrected, $p < .05$).
Results: Main effects of group were observed in left and right middle and superior temporal regions, left cerebellum, and bilateral thalamus. ESZ demonstrated greater thalamic connectivity with all middle and superior temporal regions, and reduced connectivity with cerebellar and thalamic regions. Compared to HCs, CHR demonstrated greater thalamic connectivity with one left and one right middle temporal region, and reduced connectivity with cerebellar and thalamic regions. Compared to CHR, ESZ displayed significantly greater connectivity in all but one middle/superior temporal region, but not cerebellar and thalamic regions.
Conclusions: Like chronic patients, ESZ demonstrate hyperconnectivity between the thalamus and sensory regions, and hypoconnectivity with the cerebellum. Further, CHR demonstrate intermediate levels of dysconnectivity, with mean values falling between ESZ and HC. These findings suggest that thalamic dysconnectivity occurs prior to illness onset, but is more pronounced in the early stages of schizophrenia.
Supported By: R01 MH076989
Keywords: Clinical High Risk for Psychosis, Schizophrenia, Functional Connectivity, Thalamus

F225. Structural and Tractography Analysis of Clinical High Risk Subjects for Psychosis From the Sharp Study Cohort

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Background: Abnormalities of frontal and temporal lobes are often reported in schizophrenia. Here we test for their presence in individuals at clinical high risk (CHR) for psychosis. The goal was to determine whether cortical thickness (CT), surface area (SA) and integrity of several white matter tracts related to these lobes, alone or in aggregate, distinguish CHR converters (CHR-C) from CHR non-converters (CHR-NC).
Methods: Magnetic resonance images and clinical/cognitive data were acquired in 130 CHR-NC, 22 CHR-C and 92 healthy controls (NC) at the Shanghai Mental Health Center, China (NIH funded China and Harvard Medical School (HMS) collaboration). Using an internal pipeline developed at the Psychiatry Neuroimaging Laboratory (PNL), Brigham and Women's Hospital, HMS, 9 temporal and 11 frontal regions in both hemispheres and superior longitudinal (SLF), arcuate (AF), extreme capsule (ECFS) and uncinate (UF) white matter fascicles were assessed.
Results: Temporal lobe: The posterior region of superior temporal sulcus and Heschl's gyrus CT were smaller in CHR-C compared to CHR-NC ($p=0.027$) and NC ($p=0.002$). Middle temporal gyrus (MTG) CT was also smaller in CHR-C than NC ($p=0.004$) and they were trend level for CHR-NC ($p=0.098$). Frontal lobe: The pars triangularis CT was smaller in CHR-C vs CHR-NC ($p=0.02$) and NC ($p=0.012$). In CHR-C, CT of MTG correlated with Verbal Learning ($rho=0.64$; $p=0.002$) and Visual Memory Tests ($rho=0.6$, $p=0.004$). These correlations were not present in NC or CHR-NC. Data from tractography are in progress.
Conclusions: Results suggest that language circuits distinguish CHR-C from CHR-NC and are among the earliest regions affected.
Supported By: NIMH
Keywords: Clinical High Risk for Psychosis, Tractography, Cognition, Structural MRI

F226. The Relationship Between Cortical Glutamate and Striatal Dopamine Function in Psychosis: A Multi-Modal PET and MRS Imaging Study in First Episode Psychosis

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Background: The pathophysiology of psychosis remains incompletely understood. It has been proposed that disruption in cortical glutamatergic signalling may cause aberrant striatal dopamine function and the onset of psychosis, but this has not been tested in vivo. We therefore aimed to test the relationship between glutamate function, dopamine function, and symptoms in patients with first episode psychosis.
Methods: Twenty-eight people with first episode psychosis received an 18F-DOPA positron emission tomography scan (measuring striatal dopamine synthesis capacity), and proton magnetic resonance spectroscopy (measuring cortical glutamate levels). Symptom severity was measured using the

Positive and Negative Syndrome Scale (PANSS), and functioning was assessed using the Global Assessment of Functioning (GAF).
Results: Cortical glutamate and striatal dopamine synthesis capacity were negatively correlated (r= -0.40, p<0.05). Psychotic symptoms were positively correlated with striatal dopamine synthesis capacity (r=0.38, p<0.05) and negatively correlated with cortical glutamate levels (r=-0.41, p<0.05).
Conclusions: Our findings are consistent with the hypotheses that frontal glutamate dysfunction leads to subcortical dopamine disinhibition and psychosis, and that modulation of glutamatergic pathways may show promise in the treatment of psychotic disorders.
Supported By: Medical Research Council, Wellcome Trust
Keywords: Dopamine, Glutamate, Psychosis, Positron Emission Tomography, Magnetic Resonance Spectroscopy

F227. The State or Trait Component of Dopamine and Glutamate Dysfunction in the Risk for Psychosis: An in Vivo Multimodal Imaging Study of Individuals With 22q11 Deletion

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Background: Advances in in vivo imaging studies have provided further evidence of dopaminergic and glutamatergic dysregulation in schizophrenia. Despite this, the degree to which these alterations are trait markers linked to genetic risk for psychosis or reflects state changes is not clear from previous studies. Individuals with 22q11.2 deletion have 30 -fold increase for developing psychosis. The aims of our study were to investigate dopaminergic and glutamatergic function in individuals with 22q11.2 deletion.
Methods: 21 antipsychotic naive individuals with 22q11 deletion and 26 healthy volunteers received 18F DOPA PET. A Patlak analysis was applied to calculate influx constants (Ki values) for the whole striatal ROI relative to uptake in the cerebellar reference region. 17 individuals with 22q11.2 deletion and 30 healthy controls had MRS. Voxels were placed on the anterior cingulate cortex and left striatum. Spectra were analyzed using LC Model version 6.3-1L.
Results: DSC in the whole striatum was significantly increased in the individuals with 22q11 deletion compared to healthy controls (Cohen's d= 1.47, p< 0.000). No difference was found between groups in Glx levels in anterior cingulate cortex and left striatum (p=0.29; p=0.86, respectively). Psychopathology scales were not correlated with either dopaminergic or glutamatergic function in the group of 22q11.
Conclusions: Our findings provide evidence that DSC has a strong trait component and glutamatergic dysfunction may be most likely associated with disease status. Future studies with longitudinal design are warranted to further investigate the role of dopamine and glutamate in individuals with 22q11.2 deletion.
Supported By: MRC
Keywords: 22q11.2, Dopamine, Glutamate, Schizophrenia

F228. Functional Activation Abnormalities Following Stress in At-Risk Individuals

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Background: Stress is a major risk factor for almost all psychiatric disorders, however, the underlying neurobiological mechanisms remain largely elusive. In healthy individuals, a successful stress response involves an adequate neuronal adaptation to a changing environment. This adaptive response may be dysfunctional in vulnerable individuals, potentially contributing to the development of psychopathology.
Methods: In the current study, we investigated how acute stress affects brain responses to emotional stimuli in healthy controls and whether this is affected in at-risk individuals. An fMRI study was conducted in healthy male controls (N = 39) and unaffected healthy male siblings of schizophrenia patients (N = 39) who are at increased risk for the development of a broad range of psychiatric disorders. Brain responses to pictures from the International Affective Picture System (IAPS) were measured 33 minutes after exposure to stress induced by the validated Trier Social Stress Test (TSST) or a control condition and analyzed using a 2 (control/sibling) by 2 (stress/no-stress) full factorial ANOVA.
Results: Stress differentially affected brain responses of schizophrenia siblings versus controls. Specifically, control subjects, but not schizophrenia siblings, showed reduced brain activation in key nodes of the default mode network and salience network as well as the STG, MTG, MCC, vlPFC, precentral gyrus, and cerebellar vermis in response to all pictures following stress.
Conclusions: These results indicate that even in the absence of any psychiatric symptoms, at-risk individuals display abnormal functional activation following stress which in turn may increase their vulnerability and risk for adverse outcomes.
Keywords: Psychosocial Stress, Functional Neuroimaging, Schizophrenia, Emotional Processing, Cortisol

F229. Cannabinoid 1 Receptor and Memory Function in First Episode Psychosis: A Multi-Modal PET-fMRI Study

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Background: The neurobiology of memory deficits remains poorly understood and unaddressed by current treatments. The cannabinoid 1 receptor (CB1R) modulates memory by altering mitochondrial function as well as synaptic transmission and plasticity. We investigated memory and CB1R availability, for the first time as far as we're aware in vivo. We also investigated whether memory impairments in FEP are linked to CB1R dysregulation.
Methods: Sixty-eight volunteers (33 FEP and 35 controls) completed the Sternberg working memory paradigm during an fMRI scan. A subset of these volunteers (20 FEP and 20 controls) underwent a [11C]MePPEP PET scan with arterial blood sampling.
Results: FEP patients showed decreased CB1R availability in the hippocampus, (Hedge's g=0.85), anterior cingulate (ACC) (Hedge's g=0.81) and orbitofrontal cortex (OFC) (Hedge's g=0.67). OFC CB1R was inversely correlated with positive symptom severity (R=-.672, p=0.001). FEP showed greater bilateral hippocampal activation during memory encoding using a whole-brain analysis (pFWE<0.05). Mean hippocampal activation during memory encoding was positively associated with CB1R in the anterior cingulate in controls (R=0.462, p=0.040) but not patients (R=-.210, p=0.374).
Conclusions: Consistent with evidence that CB1R in the medial prefrontal cortex modulates memory in animals, we showed that ACC CB1R availability is linked to hippocampal activation during memory encoding in controls. These findings are consistent with evidence that CB1R regulate synaptic transmission and plasticity involved in memory. The association between ACC CB1R availability and memory function is altered in FEP in the context of decreased ACC CB1R availability and altered functional activation during memory encoding.
Supported By: METSY FP7 EU grant
Keywords: Positron Emission Tomography, First Episode Psychosis (FEP), Endocannabinoids, Neuroimaging

F230. Glutamatergic Neurometabolite Levels in Patients With Treatment-Resistant Schizophrenia: A Cross-Sectional 3T Proton MRS Study

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Background: In terms of response to antipsychotic treatment, patients with schizophrenia can be classified into three groups; (1) treatment-resistant patients who are clozapine (CLZ)-resistant (ultra treatment-resistant schizophrenia [UTRS]), (2) treatment-resistant patients who are CLZ-responsive (TRS), and (3) patients who respond to non-CLZ antipsychotics (treatment non-resistant schizophrenia [TnRS]). The aim of this study was to examine glutamatergic neurometabolite levels in these three patient groups, along with healthy controls (HCs), using proton magnetic resonance spectroscopy (1H-MRS).
Methods: Glutamate (Glu) and glutamate+glutamine (Glx) levels were assessed in the associative striatum (Str), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) using 3T 1H-MRS (PRESS, TE=35ms). Neurometabolite levels were corrected for cerebrospinal fluid proportion.
Results: A total of 100 participants (26 UTRS, 27 TRS, 21 TnRS, and 26 HCs) were included in this study. Patients with UTRS showed higher Glx levels in the ACC compared to HCs (p=0.038). When patients with UTRS and TRS were combined into one group, this subset of patients showed higher Glu and Glx levels in the ACC compared to HCs (p=0.028 and p=0.023, respectively). There were no significant group differences in the Str or DLPFC.
Conclusions: Previous findings reporting higher glutamatergic levels in the ACC of patients with TRS may be mainly influenced by patients with CLZ non-responder. Higher ACC glutamatergic neurometabolite level may be a biological trait of resistance to the first-line antipsychotic treatment that is retained even after CLZ administration.
Supported By: CIHR, OMHF, NARSAD
Keywords: Treatment Resistant Schizophrenia, Glutamate, Magnetic Resonance Spectroscopy

F231. Microstructural Changes in White Matter Associated With Alcohol Use in Early Phase Psychosis: A Diffusion Tensor Imaging (DTI) and Relaxometry Study

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Background: Accumulating evidence suggests that brain white matter (WM) abnormalities may be central to the pathophysiology of psychotic disorders. Additionally, cannabis use and alcohol use are each associated with WM abnormalities, however there is limited data on these substances effects on WM microstructure in psychosis, especially early phase psychosis (EPP). This study examined the impact of cannabis use and alcohol use in WM in EPP (N=21) using diffusion tensor imaging (DTI) and transverse relaxation time of tissue water (T2), with the primary outcomes being mean fractional anisotropy (FA) and T2.
Methods: Analyses were performed at the full brain level using tract-based spatial statistics (TBSS) analysis as well as within a predefined WM region of interest (ROI) implicated in psychosis (containing the left superior longitudinal fasciculus).
Results: Our findings revealed that younger age of onset of regular alcohol use (greater than one drink per week) was associated with lower FA values in the left thalamic radiation, left parahippocampal and left amygdalar WM. Also, more frequent lifetime cannabis use was correlated with increased mean full brain FA, although this finding did not survive correction for multiple comparisons. There was no significant relationship found between FA and alcohol or cannabis use within the ROI. Relaxometry analysis revealed trend level evidence of shortened T2 with more frequent cannabis use.

Conclusions: This study provides novel data demonstrating cortical and subcortical WM changes related to alcohol use in EPP and is the first to combine DTI and relaxometry as it relates to this patient population.
Supported By: Dalhousie Psychiatry Research Fund
Keywords: Early Psychosis, Alcohol, Cannabis, Diffusion Tensor Imaging (DTI), T2 Relaxometry

F232. Abnormality of Resting-State Functional Connectivity in Insular Cortex in Patients With First Episode Psychosis

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Background: The insula is involved in detecting the salience of internal and external stimuli, and it plays a critical role in psychosis. To acquire a full picture of the functional alterations of the insula in psychosis, we examined the insula cortical functional connectivity (FC) in patients with first episode psychosis (FEP) and explored the relationship between the connectivity and the neuropsychological function.
Methods: In this study, 84 patients with FEP and 84 individually age- and sex-matched healthy controls (HC) completed resting-state functional MRI, neuropsychological testing, and social cognition assessments. To investigate the functional connectivity values, we computed inter-parcel correlations between insula and another ipsilateral cortical regions in the participants.
Results: In the posterior insula, the FEP patients exhibited decreased FC between the right posterior insula and the right middle fronto-orbital gyrus ($P<0.001$). In the anterior insula, on the other hand, the FEP patients exhibited increased FC between the right anterior insula and the right cerebellum ($P=0.001$). In addition, the FC between the right posterior insula and the right middle fronto-orbital gyrus were negatively correlated with the social cognition in the measures of Recognition reaction time ($r=-0.240$, $P=0.003$), and Memory reaction time ($r=-0.221$, $P=0.006$).
Conclusions: The results suggested that the right insula might play an important role in the pathological mechanism of psychosis and the dysfunction of insula might disturb the neuropsychological and social cognitive dimensions in a wide range of psychiatric disorders with psychosis.
Supported By: NIH
Keywords: First Episode Psychosis (FEP), Functional Connectivity, Social Cognition, Schizophrenia

F233. Magnetic Resonance Imaging Study of the Cerebellum in Schizophrenia: Effects of Ageing, Obesity, and Other Health Risk Factors

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Background: Cerebellar atrophy is well documented in schizophrenia by post-mortem as well as in-vivo brain imaging studies. Vermal atrophy is most commonly reported. Most studies, however, do not account for health risk factors commonly present in schizophrenia, such as obesity, diabetes, hypertension, smoking, and other substance use which is limiting life expectancies and also leading to brain atrophy.
Methods: We investigated high-resolution MPRAGE magnetic resonance images (1.5T Siemens Avanto) from 297 schizophrenia patients and 230 healthy subjects. Images were preprocessed with Freesurfer 5.3 and cerebellar anatomical boundaries identified with reference to the SUIT atlas. Intracranial volumes were used to correct anatomical volumes. The final analyses consisted of $N=134$ subjects in each group matched for gender (67f/67m) and age (mean: 39.4 years; range: 18-65 years).
Results: We found a small reduction of total white matter volumes in the schizophrenia group ($P=0.039$), which was not confirmed when adding age, being overweight, and other risk factors to the statistical model. Age accounted for the largest effect on total cerebellar as well as total grey matter volumes ($P<0.0001$ respectively), followed by being overweight for total grey matter volume ($P<0.001$). The multivariate analysis of regional grey matter revealed a significant group difference for vermis, left Crus I and right IX ($P=0.030$) accounting for 16% of the variance compared to 29% for age, 13% for being overweight, and 11% for other health risks combined.
Conclusions: Our results emphasise the importance of controlling for common health risk factors when interpreting brain imaging data of people with schizophrenia.
Supported By: Schizophrenia Research Institute
Keywords: Cerebellum, Structural Magnetic Resonance Imaging, Schizophrenia, Schizoaffective Disorder, Obesity, Age

F234. Inflammation, Guanosine Triphosphate Cyclohydrolase-1 and Kynurenine Metabolic Pathways in Patients With Schizophrenia

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Background: We have previously observed elevated serum phenylalanine (Phe) and phenylalanine/tyrosine (Phe/Tyr) ratio in patients with schizophrenia, findings suggestive of an immune-related guanosine triphosphate cyclohydrolase-1 metabolic pathway (GTPCH-1) abnormality. The kynurenine (Kyn) pathway, mainly driven by immune activation, is another pathway implicated in the pathophysiology of schizophrenia. However, we did not have any measure of immune activation in our previous study. We now aimed to

simultaneously evaluate the GTPCH-1 and Kyn pathways in relation to neopterin (a marker of immune activation) in patients with schizophrenia.
Methods: 106 adult patients with schizophrenia were recruited. Fasting plasma tryptophan (Trp), Kyn, Phe, and Tyr were measured by HPLC while neopterin was measured by ELISA. Phe/Tyr and Kyn/Trp ratios were computed as proxy measures of activity of key enzymes in the GTPCH-1 and Kyn pathways respectively. Partial correlations (i.e. correlations adjusted for age, sex, race and BMI) between neopterin and the amino acids, Kyn, and the ratios were calculated.
Results: Neopterin negatively correlated with Trp ($r=-0.30$, $p=0.031$), but positively correlated with Kyn, Kyn/Trp ratio and Phe/Tyr ratio ($r=0.43$, $p<0.001$; $r=0.67$, $p<0.001$; $r= 0.21$, $p=0.05$ respectively), but did not correlate with Phe, Tyr.
Conclusions: The results of the current study are consistent with the idea that our previous finding of elevated Phe/Tyr ratio in patients with schizophrenia is driven by inflammation. The GTPCH-1 and Kyn pathways are related to immune activation in schizophrenia.
Keywords: Schizophrenia, Inflammation, Inflammatory Cytokines, Guanosine Triphosphate Cyclohydrolase-1, Kynurenine Pathway

F235. Immune and Infectious Biomarkers in Psychosis and Clinically High-Risk Psychosis Populations

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Background: Immune and infectious contributions to psychiatric disease have been increasingly recognized, but mechanisms are poorly understood. Anti-NMDA receptor encephalitis frequently presents with psychosis, and many studies have investigated the presence of anti-NMDAR antibodies in those with schizophrenia. Infectious diseases such as Lyme disease can present with neuropsychiatric manifestations, and co-morbid Lyme disease and psychosis has been reported in case reports.
Methods: We recruited 50 children and young adults with psychosis, 17 with clinically high risk for psychosis (CHR) and 37 unaffected with psychosis controls; some of the psychosis participants were referred from the Lyme Evaluation Service. We investigated anti-neuronal antibodies (GAD65, NMDAE, GABA-B, AQP4, LGI1 and CASPR2) by tissue and recombinant cell-based assay (CBA). We also tested for Lyme C6 antibodies (ELISA) on all participants, and followed up with Western blot analysis in any participant with a positive C6 antibody test or with a stated clinical history of Lyme disease.
Results: There were no positive anti-neuronal antibodies in any of the three groups. 14 of 50 in the psychosis group (28%) had either a positive C6 antibody test or a clinical history of reported Lyme disease. 3 of 50 were C6 antibody positive in the psychosis group (6%) compared to 1 of 17 in the CHR (5.8%), and 0 of 37 controls. Western blot serology was CDC positive for Lyme disease only in the psychosis group, 4 of 50 (8%).
Conclusions: The significance of this association between Lyme disease and psychosis is interesting but unclear; it warrants further investigation with an epidemiological study.
Supported By: AACAP grant
Keywords: Early Psychosis, Anti-Neuronal Antibodies, Lyme Disease, Brain-Immune Axis

F236. Association of Baseline Tumor Necrosis Factor and the Development of Negative Symptoms in Individuals at Clinical High Risk for Psychosis

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Background: Negative Symptoms are core symptoms of schizophrenia and other psychotic disorders. Understanding predictors of negative symptoms in the clinical high-risk (CHR) state of psychosis is necessary to investigate risk factors for these symptoms. Previous work from the North American Prodromal Longitudinal Study (NAPLS) cohort has demonstrated that inflammation may be related to the development of psychosis in CHR subjects, which supports a literature showing an association between inflammation and psychopathology of schizophrenia, including negative symptoms.
Methods: Concentrations of Interleukin (IL)-1 receptor antagonist (IL-1RA), IL-4, IL-6, IL-8, Interferon-gamma (IFN-g), and Tumor Necrosis Factor (TNF) were examined at baseline. The scale of Prodromal Symptoms (SOPS) was assessed at baseline, 6, 12, 18, and 24 months. Stepwise linear regression models were calculated to explore the relationship between negative symptom and inflammatory markers. Baseline negative symptoms, scores on the Calgary Depression Scale for Schizophrenia, sex, age, and race were included as covariates.
Results: 80 CHR individuals at baseline (54M, 26F) from the NAPLS cohort were included. Baseline TNF (mean = 0.87pg/ml, sd = 0.38) predicted the decreased expression of emotion item of the SOPS at 6 month ($n=54$; $beta=0.25$, $p=0.011$) and 12 month ($n=48$; $beta=0.39$, $p=0.001$).
Conclusions: Baseline TNF predicted negative symptom on the SOPS, including anhedonia, apathy, and loss of interest at the 6 month and 12 month follow-up visits, even when controlling for depression and other covariates. This suggests that TNF may be involved in the development of negative symptoms in CHR individuals and could be a potential treatment target.

Supported By: U01MH081988-09 (EFW), UL1TR002378, and KL2TR002381.
Keywords: Clinical High Risk for Psychosis, Negative Symptoms, Tumor Necrosis Factor, Inflammation, Anhedonia

F237. Increased Circulating Regulatory T Cells in Medicated People With Schizophrenia

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Background: Immunological abnormalities in people with schizophrenia are increasingly reported. CD4+/CD25+/Foxp3+ regulatory T cells (Tregs) are key immunoregulatory cells involved in the control inflammatory processes, including autoimmune and hypersensitive reactions; their functions are directly related to the HLA gene, implicated in the disease by genetic studies. However, T-reg status in people with schizophrenia has not been previously reported
Methods: The proportion of circulating Tregs was examined using flow cytometry along with cytological and psychometric analyses, in participants with a DSM-5 diagnosis of schizophrenia (N=26) and healthy controls (N=19). Psychiatric symptoms and cognitive function were evaluated using the Scale for the Assessment of Negative Symptoms (SANS), the Brief Psychiatric Rating Scale (BPRS), and the MATRICS Cognitive Battery (MCCB)
Results: Increased proportions of Tregs from the CD4+ population were observed in schizophrenia compared to controls. No differences were observed in total leukocyte counts and CD3+ or CD4+ T cells confirming a specific effect for the Treg population. Moreover, the ratio of activated Tregs (CD45Rneg) was comparable in both groups suggesting that increased Tregs are not the result of dysfunctional Tregs. Higher Tregs in schizophrenia were related to fewer negative symptoms (SANS total score r=-0.4, p=0.05; alogia r=-0.5, p=0.02; affective blunting r=-0.4, p=0.07) and a trend for better attention (r=0.3, p=0.09), two core domains of the illness
Conclusions: Tregs are higher in medicated people with schizophrenia with higher levels associated with lower negative symptoms and better cognitive function. These results suggest that immunoregulatory functions of Tregs may contribute to improved symptoms in schizophrenia
Supported By: NIMH grant Silvio O. Conte Centers for Basic Neuroscience or Translational Mental Health Research P50 MH103222
Keywords: Inflammation, Cognitive Deficits, Negative Symptoms, T Cells, Clozapine

F238. Plasma Tumor Necrosis Factor-Alpha Correlates With L-Selectin in Patients With Schizophrenia

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Background: Immune dysregulation with abnormal levels of cytokines have been implicated in the pathophysiology of schizophrenia. The proinflammatory cytokine tumor necrosis factor-alpha (TNF-α), has been suggested to be a trait marker in schizophrenia. Entry of leukocytes into tissues is a key feature of inflammation, a process involving E-, L-, and P-selectins. Our group has previously reported abnormal levels of the leukocyte adhesion receptor, L-selectin, in patients with multi-episode chronic schizophrenia. We aimed to evaluate the relationship between plasma TNF-α and L-selectin in patients with schizophrenia.
Methods: 106 patients with schizophrenia (diagnosed with MINI) were recruited. Fasting plasma TNF-α and L-selectin were measured using ELISA. Spearman's correlation was used to assess the relationship between TNF-α and L-selectin. 77 patients (mean age 32.9 (SD =12.28), 72% male, 52% Black, 31% White, 15% Hispanic, 2% Asian) had complete data.
Results: TNF-α positively correlated with L-selectin (rho=0.32, p=0.005), a finding which persisted after adjusting for age, sex and race (partial rho= 0.34, p=0.003).
Conclusions: Recent studies have demonstrated that L-selectin reduces premature activation of neutrophils to ensure clearance of pathogens and wound healing without excessive tissue injury. It is therefore possible that increase in L-selectin in tandem with TNF-α is a protective mechanism in schizophrenia, a hypothesis that requires further study.
Keywords: Biomarkers, Schizophrenia, Tumor Necrosis Factor Alpha, L-selectin, Inflammatory Cytokines

F239. Role of Lymphocyte Subsets and T-Cell Profiles in the Immune Dysfunction of Schizophrenia

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Background: Schizophrenia has been associated with increased level of inflammation. An investigation of immune cell subsets and T-cell activation profiles might be helpful to understand the mechanism of the immunopathogenesis in schizophrenia.
Methods: In order to evaluate specific subsets, cells were stained with combinations of the following monoclonal human antibodies: anti-CD14, anti-CD3, anti-CD4, anti-CD8, anti-CD19, anti-CD20, anti-CD16/56. PBMC were isolated and stained with the human FoxP3 kit containing anti-CD4/anti-CD25 and intracellular anti-Foxp3 on day 0 and day 3. PBMCs were cultured for 72 hours and stimulated with anti-CD3. Cytokines were measured from plasma samples and the culture supernatant by using Th1/Th2/Th17 cytokine bead array kit.
Results: 41 stable-chronic subjects (mean age= 41,09, 41.5% female) with schizophrenia (all medicated) and 40 age-sex-

smoking-BMI status matched controls (mean age=40.8, 40% female) were recruited in this study. Patients showed a higher percentage of CD14+ ($p<0.05$), CD19+ ($p<0.05$), CD20+ ($p<0.05$), CD4+CD25+ ($p<0.001$), CD4+CD+25FoxP3 ($p<0.001$) cells and a lower percentage of CD3+ ($p<0.001$), CD3+CD4+ ($p<0.001$) cells compared to controls. After stimulation percentage of CD4+CD25+($p<0.001$) cells was found still significantly higher ($p<0.001$). Furthermore, supernatant cytokine panel was associated with high levels of IL-4 ($p<0.05$), IL-6 ($p<0.001$), IL-17a ($p<0.001$), TNFa ($p<0.001$), IFNg ($p<0.001$). Additionally, plasma levels of IL-4 ($p<0.05$), IL-6 ($p<0.001$) and IL-17a ($p<0.05$) were found significantly higher in patients than controls.

Conclusions: Our data suggest that high level of T cell activation with dysfunction of T regulatory cells (CD4+CD25+ FoxP3) and change of Th cell profiles might cause an imbalance in T cell-mediated immunity and high level of inflammation in schizophrenia.

Supported By: Yeditepe University Internal Funding, Istanbul, Turkey; Marmara University Internal Funding, Istanbul, Turkey

Keywords: Schizophrenia, Inflammation, T Cells, T Regulatory Cells

F240. Cytokine Levels are Associated With Slowed Latency of Acoustic Startle and Slowed Processing Speed in Schizophrenia

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Background: Recent findings indicate that patients with schizophrenia (SCZ) have increased cytokines compared to healthy controls (CON), due to immune activation or response to an infection such as Toxoplasma gondii (TOXO). Latency of the acoustic startle response, a putative index of neural processing speed, is slower in SCZ than CON, and slower in TOXO seropositive SCZs as compared to those without TOXO. We investigated the relationship of cytokine levels with slowing of startle latency and slowed speed of processing.

Methods: The subject sample consisted of 171 SCZ and 127 CON subjects. Subsets were tested on a standard acoustic startle paradigm designed to measure startle magnitude and latency, cytokine levels were assayed from venous blood, and speed of processing (SoP) was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB).

Results: Latency was slower ($F(1,142)=6.65$, $p=0.01$) and processing speed was impaired ($F(1,114)=45.11$, $p<0.001$) in SCZ compared to CON. Higher cytokines levels were associated with slower latency (IL-2, IL-6, IL-12, IL-1Beta, MCP-1, MIP-1alpha, IL-1RA, p-values<0.05). Higher cytokines levels were also associated with slower SoP (IL-12, interferon-alpha, interferon-gamma, MCP-1, MIP-1alpha, IL-1RA, and others, p-values<0.05). Slower latency was correlated with slower SoP ($r=-0.30$, $p=0.002$).

Conclusions: These findings confirm an association of elevated cytokines with cognitive slowing, and extend this finding to slower latency of acoustic startle, an index of neural processing speed, in a sample of SCZ and CON subjects. We speculate that inflammation as evidenced by cytokine elevation may underlie both slowing of startle latency and slowing of processing speed.

Supported By: Veterans Administration Merit Review Grant (Duncan); 1R01MH092512-01 and R21MH083138-01A1 (Pearce)

Keywords: Schizophrenia, Inflammatory Cytokines, Acoustic Startle Latency

F241. Super-Resolution Diffusion Weighted Imaging in Schizophrenia

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Background: While developments in neuroimaging have made it one of the most common non-invasive tools in humans, a gap still remains in the ability to resolve fine anatomical features, where abnormalities may occur in psychiatric illness. One core issue contributing to this gap is spatial resolution. Particularly, diffusion weighted imaging (DWI) is a resolution-starved method given the size of individual axons through which water molecules diffuse. Track density imaging (TDI) offers a novel approach to this obstacle through post-acquisition DWI processing techniques.

Methods: TDI methods were performed on multi-shell DWI data for patients with schizophrenia (N=40) and a demographically matched control group (N=40). All scans were acquired on a Siemens 3T scanner. Neuroimaging data were preprocessed via Human Connectome Project pipelines. Preprocessed data were fed into FSL's bedpostx to build distributions of voxel-wise diffusion properties and model crossing fibers. A continuous representation of brain tractography was then created using information from neighboring voxels.

Results: We achieved post-processing supra-spatial resolution (1.0 mm, 0.25 mm, and 0.125 mm) beyond that of the original voxel (1.8 mm isotropic). Results were completed for specific thalamic nuclei in SCZ patients, indicating that TDI techniques can be applied to clinical populations.

Conclusions: TDI yielded unprecedented anatomical precision from standard mutli-shell DWI data, demonstrating the potential for this innovative technique to bridge the gap in resolution-starved neuroimaging modalities. Increasing spatial resolution by an order of magnitude offers new possibilities for informing diagnosis and treatment, particularly in relation to anatomical detail that may be otherwise beyond reach.

Supported By: BlackThorn Therapeutics

Keywords: Diffusion MRI, Track Density Imaging, Super-resolution, Schizophrenia

F242. Intensive Longitudinal Assessment of Mania and Psychosis Using Commonly Available Technologies

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Background: Individuals with affective and psychotic illnesses often experience profound changes in mood and cognition over time, and over relatively short periods (e.g., hospitalization). The nature of these fluctuations often vary significantly from individual to individual, posing tremendous challenges for clinical practice and group comparison studies. And yet, patterns often emerge within an individual, allowing clinicians to optimize treatment over longitudinal assessments.
Methods: Intensive, longitudinal data acquisition from smartphones, wrist-worn actigraphy devices, and audio-visual (AV) data from study visit encounters, provides rich, complementary data about individual behavioral patterns that can be used to optimize models of illness prediction. We assessed individuals with affective and non-affective psychosis in naturalistic settings over extended periods (>1 year) to study individual patterns of baseline and illness-related behavior.
Results: We collected over 100 months of continuous data from 12 participants, including >100 study visits, >60 MRI scans, >1Billion actigraphy data points, and >100K hours of GPS, demonstrating that patients with even severe mental illness can be studied naturalistically for extended periods to track illness fluctuations relative to changes in multivariate behavioral data. We discovered aberrant relationships between changes in sleep and energy in affective psychosis patients, as an example of one of many behavioral illness markers not captured by conventional assessments.
Conclusions: N-of-1 case series collected from single patients in naturalistic settings using commonly available sensors has the potential to pave the way for closed-loop illness detection systems and adaptive neurobiological sampling strategies that could transform our approach to developing personalized therapeutics in psychiatry.
Supported By: Harvard Brain Science Initiative
Keywords: Longitudinal Study, Pervasive Sensing, Schizophrenia, Bipolar Disorder, Machine Learning

F243. Behavioral Inhibition and Psychotic-Like Experiences in a Non-Clinical, Young Adult Sample

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Background: There is evidence that individual differences in the sensitivity of both the behavioral inhibition and activation systems (BIS/BAS) may increase risk for a variety of mental disorders. Yet, few studies have examined the relationship between BIS/BAS and the occurrence of psychotic-like experiences (PLEs), despite evidence that both are related to common correlates of PLEs, such as anxiety and depression. We hypothesized that both BIS/BAS sensitivities would be associated with PLEs in a non-clinical, young adult sample.
Methods: Undergraduates (N = 1122) were administered the Prodromal Questionnaire to measure PLEs and the BIS/BAS scales to measure BIS/BAS sensitivities. Bivariate correlations were performed to test relationships between PLEs, BIS/BAS sensitivities, and potential covariates. Given that age was related to all three variables of interest, multiple regressions were performed in order to test these relationships while holding age constant.
Results: After controlling for age, a positive relationship was found between BIS sensitivity and PLEs, $\beta = .28$, $p < .001$, and no relationship was found between BAS sensitivity and PLEs, $\beta = -.04$, $p = .18$.
Conclusions: The finding that BIS and PLEs are related appears to be novel and may indicate that individuals who report more BIS sensitivity s may be at increased risk for psychological symptoms beyond mood and anxiety disorders, such as PLEs.
Keywords: Psychotic Disorders, Behavioral Activation & Inhibition, Non-clinical Sample

F244. Aggression in First Episode Psychosis: Characteristics and Associated Factors

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Background: The early stages of psychosis are associated with high rates of aggression. We aim to determine the rate of aggressive behavior in first episode psychosis patients, to characterize the type of aggression and to study the clinical characteristics associated with aggressive behavior.
Methods: We have conducted a retrospective review of clinical charts to examine the rates of aggressive behaviors in 450 individuals FEP (first episode psychosis) and 125 CHR (clinical high risk).
Results: 56% (n=320) reported a history of aggressive behavior. 50% showed aggression toward others, 18% aggression towards self and others, and 8% aggression towards objects only. Aggressive behavior was predominantly physical (53%), although many individuals also demonstrated both physical and verbal aggression (32%). Proactive aggressive behavior was shown in 33.3% while reactive aggressive behavior was shown in 61.1%. The duration of untreated psychosis was longer in non-aggressive subjects. Aggressive behavior was associated with learning

problems (p=0.001) and developmental delay (p=0.05). Birth complications and a history of neurological conditions were associated with aggressive behavior.
Conclusions: Aggression is common in early psychosis, for both FEP and CHR, particularly reactive aggression. Aggression in first episode psychosis is associated with a variety of clinical factors, including duration of untreated psychosis, learning and developmental problems and birth complications. Aggression in psychosis has been associated with delayed or inadequate treatment, but the development of appropriate targeted interventions must be mediated by an understanding of factors underlying aggressive behaviors.
Supported By: NIMH
Keywords: First-Episode Psychosis (FEP), Aggression, Neurodevelopmental Trajectories

F245. Hallucinations and Self-Generated Imprecision: A Markov Decision Process Model of Auditory Hallucinations

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Background: Auditory verbal hallucinations (AVH) are often distressing symptoms of several neuropsychiatric conditions. The information processing deficits underlying AVH are not yet clear. Using a Markov Decision Process, a Bayesian Active Inference model, we have produced a novel, neurobiologically-informed model of AVH as false (positive) inferences.
Methods: We simulated an agent that could infer two types of hidden states: it could either listen or not listen to a voice and it could be speaking or not speaking. The agent could also infer the policies (i.e. sequences of speaking or listening) it was pursuing. The sensory data available to the agent consisted of auditory or proprioceptive inputs. Using this model, we have observed that low sensory precision (i.e. increased estimated variance of sensory data) combined with a reduced policy space (which may be related to dysfunctional cortico-striatal connections), produces hallucinations. Here, we sought to examine whether reducing the policy space of an agent that can infer its own sensory precision might cause modulation of sensory precision.
Results: We found that given a diminished initial sensory precision, agents with reduced policy spaces downmodulate their sensory precision even further, producing hallucinations.
Conclusions: This suggests that agents with impoverished models of the world reduce their weighting of sensory information when the latter is of little benefit to perceptual inference. This results in the emergence of hallucinations that conform to their prior beliefs. Our model could be verified empirically using dynamic causal modelling of imaging data and animal models.
Supported By: Richard and Edith Strauss Fellowship
Keywords: Computational Psychiatry, Schizophrenia, Auditory Hallucination

F246. Sleep Quality and Clinical Improvement in First Episode Psychosis

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Background: Sleep disturbance is a common feature in early psychosis. Understanding sleep quality in early psychosis can be beneficial in determining interventions for coordinated specialty care (CSC). We investigated the association between subjective sleep quality, clinical symptoms and clinical response.
Methods: 48 young persons ages 16-35 years with onset of psychosis within 3 years prior underwent 2-years of CSC. Rating scales included sleep quality (PSQI), anxiety (BAI), depression (BDI-II), affective states (PANAS), and clinical improvement (CGI-I) administered at intake, 3 months and 6 months. Participants provided informed consent. Correlational analyses were performed on changes in PSQI (slope) BAI, BDI-II, PANAS-negative, PANAS-positive over 3 assessments. Analysis were stratified by improvement − CGI-I <2 (much improvement) (n=17) and CGI >3 (little/no improvement) (n=21).
Results: Analyses of sleep quality and clinical improvement included participants with three PSQI ratings. Overall PSQI ratings did not change significantly over time. BAI and BDI-II scores significantly decreased over time. There was a trend for positive correlations among PSQI, and BAI and BDI-II scores. Stratified by improvement, those rated 'much improved' experienced greater reduction of PSQI scores.
Conclusions: We found improved sleep quality in those with global clinical improvement over 6 months of CSC. Sleep quality correlated with reduced depression and anxiety. Although these findings do not address direction of causality, our findings indicate that improving sleep quality should be a specific focus in early psychosis treatment.
Supported By: SAMSHA MH block grant
Keywords: Sleep, First Episode Psychosis (FEP), Schizophrenia, Depression, Anxiety

F247. The Relationship Between Sleep, Dissociation, and Psychotic-Like Experiences

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Background: Sleep disturbances have frequently been associated with the full spectrum of psychosis, from psychotic-like experiences (PLEs) to individuals who meet diagnostic criteria for schizophrenia. Similarly, dissociative experiences have been linked to sleep disturbances and PLEs. The aim of this study was to examine the role of dissociation in the relationship between sleep quality and PLEs.

Methods: PLEs, dissociative symptoms, and sleep quality were examined in 1,677 undergraduate students using self-report measures. A mediation analysis using PROCESS was performed to examine whether dissociative experiences can account for some of the relationship between sleep quality and PLEs.
Results: Dissociative symptoms significantly mediated the relationship between sleep quality and PLEs, with both age and gender used as covariates, CI: [.1513, .2840].
Conclusions: These findings suggest that dissociation may be a key contributor to the relationship between disrupted sleep and PLEs, which could have treatment and identification implications.
Supported By: This work was funded by CLA Research Award, Temple University, Philadelphia, PA (L.M.E.), a start-up grant awarded to L.M.E., and the National Institute of Mental Health (MH096478, Principal Investigator L.M.E.).
Keywords: Early Psychosis, Sleep, Dissociation

F248. Suicidal Behaviors and Non-Suicidal Self-Harm in a Schizophrenia Sample

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Background: Lifetime risk of completed suicide and suicide attempts are high in people with schizophrenia. We assessed the prevalence and predictors of suicidal behaviors in a large sample of living schizophrenia cases and tested the associations of non-suicidal self-injury (NSSI), mood disorder, suicidal ideation, and suicide attempts.
Methods: Data on suicidal behaviors were abstracted from medical records in 570 participants diagnosed with schizophrenia or schizoaffective disorder. We used logistic regression analyses to study the relationships among NSSI, presence of mood disorder symptoms, suicidal ideation, and suicide attempts. All analyses controlled for age, sex, and race.
Results: We found a history suicidal ideation in medical records for 73.2% of participants and of suicidal attempts in 43.4%. Suicidal ideation significantly predicted attempt (p=5.1E-11, OR=4.4). Presence of a mood disorder was a stronger predictor of suicidal ideation (p=6.9E-09, OR= 3.2) than was NSSI (p=0.04, OR=1.6). However, NSSI was a stronger predictor of actual suicide attempt (p=9.631E-09, OR=3.1) than were mood disorders (p=.001, OR=1.8). When mood disorders, suicidal ideation, and NSSI were modeled together, ideation (p=7.6E-09, OR=3.9) and NSSI (p= 6.9E-08, OR=3.0) were independent predictors of attempts, whereas mood disorders were not (p=.074, OR=1.4).
Conclusions: Suicidal ideation and attempts are highly prevalent in our sample. While mood symptoms are generally viewed as critical predictors of suicide attempts, our data reaffirms that suicidal ideation mediates the relationship between mood disorders and attempts. Perhaps indicative of a separable impulsivity risk dimension, NSSI predicted attempts independently of ideation and mood.
Supported By: NIH Intramural Research Program
Keywords: Schizophrenia, Schizoaffective Disorder, Non-Suicidal Self-Injury, Suicide Attempts, Suicidal Ideation

F249. Sleep Quality, Psychological Symptoms, and Psychotic-Like Experiences

Arielle Ered[1], Shanna Cooper[1], and Lauren Ellman[1]

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Background: Poor sleep quality has been repeatedly linked to the entire psychosis continuum, including psychotic-like experiences (PLEs); however, sleep dysfunction is a component of several other psychopathologies that have also been linked to increased risk for PLEs, including depression, anxiety, and post-traumatic stress disorder (PTSD). It has yet to be examined if PLEs are a significant risk factor for poor sleep quality or if this sleep dysfunction is better accounted for by comorbid psychopathology.
Methods: In 2,687 undergraduates, PLEs were evaluated using the positive items of the Prodromal Questionnaire. Symptoms of anxiety, depression, and PTSD were also assessed, as was sleep quality. Mediation analysis using PROCESS was conducted to determine if poor sleep quality associated with PLEs was in fact more associated with symptoms of other psychopathologies.
Results: Symptoms of depression and PTSD mediated the relationship between PLEs and sleep quality [CIs= .0277 - .0498 and .0451 - .0718, respectively], though anxiety symptoms did not [CI= -.0161 - .0063].
Conclusions: These findings suggest that treating symptoms of depression and PTSD may improve multiple domains of psychotic illness.
Supported By: This work was funded by CLA Research Award, Temple University, Philadelphia, PA (L.M.E.), a start-up grant awarded to L.M.E., and the National Institute of Mental Health (MH096478, Principal Investigator L.M.E.).
Keywords: Early Psychosis, Trauma, Depression, Anxiety, Sleep

F250. Increased Dopamine Synthesis Capacity in the Ventral Striatum of Patients With Chronic Schizophrenia During Psychotic Remission

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Background: Striatal presynaptic dopamine synthesis capacity, as measured by 18fluoro-levo-dihydroxyphenylalanine positron emission tomography (18F-DOPA-PET), is increased in patients with schizophrenia, and has been suggested to be associated with psychosis. However, the majority of

18F-DOPA-PET studies in schizophrenia did not report or find such an association. Furthermore, striatal dopamine synthesis capacity is already increased in first-degree relatives of patients with schizophrenia and persons at high clinical risk of developing psychosis. Therefore, it is unclear whether presynaptic striatal dopamine synthesis capacity is increased only during psychosis in schizophrenia or also during psychotic remission.

Methods: A whole-body mMR Biograph PET/MRI scanner was used to investigate dopamine synthesis capacity (indexed as the influx rate constant Kicer) with dynamic 18F-DOPA-PET in 26 patients with chronic schizophrenia, currently in psychotic remission and 23 healthy controls. Regions-of-interest from a striatal functional atlas (limbic, associative, and sensorimotor) were co-registered to PET images. Kicer values were extracted from these regions and t-tests were conducted to investigate group differences, controlled for age, gender, and medication.

Results: In patients increased Kicer was found in the limbic striatum (0.040 ± 0.005 min-1, $p=0.02$). No other differences in regional Kicer were found between groups. In patients, limbic striatum Kicer did not correlate with clinical and cognitive scores, but in healthy controls, we found an association between limbic striatum Kicer and letter number span ($r=0.5$, $p=0.02$).

Conclusions: These findings provide evidence that presynaptic striatal dopamine synthesis capacity is increased in chronic patients with schizophrenia during psychotic remission, suggesting that presynaptic dopamine hyperfunction is not necessarily linked with psychosis.

Supported By: European Union 7th Framework Programme, TRIMAGE – a dedicated trimodality (PET/MR/EEG) imaging tool for schizophrenia (Grant no. 602621)

Keywords: Schizophrenia, FDOPA, PET Imaging

F251. Psychiatric Liability Genes are Linked to Oscillatory Brain Activity: A Genome-Wide Association Study

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Background: Oscillatory activity is crucial for information processing in the brain, and has a long history as a biomarker for psychopathology. Variation in oscillatory activity is highly heritable, but the involvement of specific genetic variants, genes, and brain expression pathways remains elusive.

Methods: We performed a genome-wide association study for the power of oscillations at frequencies (~2 Hz delta, ~6 Hz theta, ~10 Hz alpha, and ~20 Hz beta) of the eyes-closed resting electroencephalogram (EEG) for 4.5M SNPs in N=8425 subjects. Next, we performed KGG positional gene-based analysis, and brain-expression analyses.

Results: One significant SNP for alpha oscillation power is intronic to protein-coding gene PRKG2 ($p<5x10-8$). PRKG2 is deleted in the 4q21 microdeletion syndrome which results in speech and mental retardation. GABRA2—a known genetic marker for alcohol use disorder and epilepsy—significantly affected beta power, consistent with the known relation between GABAA interneuron activity and beta oscillations. Metaxcan (viz., SNP-based imputation of tissue expression levels using the GTEx expression database) revealed that hippocampal GABRA2 expression may mediate this effect. Twenty-four schizophrenia-linked genes at 3p21.1 were significant for alpha power (FDR $q<0.05$). SNPs in this region were linked to expression of GLYCTK in hippocampal tissue, and GNL3 and ITIH4 in the frontal cortex. Brain-expressed genes were significantly enriched.

Conclusions: We successfully associated genes and genetic variants with oscillatory brain activity, some of which were previously associated with psychopathology (schizophrenia, alcohol use disorders). The results show that psychopathological liability genes affect brain functioning, and linked the genes' expression to specific cortical/subcortical brain regions.

Supported By: U54 EB020403; DA 05147, DA 36216, DA 024417; NIH NIAAA U10AA00840, NIH GEI U01HG004438, HHSN268200782096C; NWO/ZonMW 904-61-090, 985-10-002, 912-10-020, 904-61-193,480-04-004, 463-06-001, 451-04-034, 400-05-717, Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192, BBMRI–NL, 184.021.007, NWO-Groot 480-15-001/674. ERC FP7/2007-2013), ENGAGE HEALTH-F4-2007-201413, ERC Advanced 230374, Starting 284167), NIMH U24 MH068457-06, NIH R01D0042157-01A, MH081802, R01 DK092127-04, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995; NWO 480-04- 004, NWO/SPI 56-464-14192, and NWO 911-09-032, NWO/MagW VENI-451-08-026; ERC-230374; BBR Foundation (NARSAD) 21668; VU-USF 96/22; HFSP RG0154/1998-B; KNAW PAH/6635; Australian Research Council A79600334, A79906588, A79801419, DP0212016; NHMRC 389891; Fellowship APP1103623; NIH K01DA037914; NIH DA 05147, DA 36216, DA 024417, AA 09367, DA 13240; U10AA008401

Keywords: Electroencephalography (EEG), GWAS, Gene Expression, Schizophrenia, Alcohol Use Disorder

F252. Effects of Glycine and D-Cycloserine on in Vivo Neuronal Activity in Normal and Schizophrenia Model Mice

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Background: NMDAR hypofunction has been proposed to underlie the pathogenesis of schizophrenia. Specifically, what has been proposed is that reduced functions of NMDARs on the GABAergic neurons during development leads to alterations in the balance between excitation and inhibition which further alters the proper development of the neural circuitry and manifested as functional phenotypes in schizophrenia. It has long been suggested, based on human studies, that compound which enhance the function/activity of NMDARs may show beneficial effects on schizophrenia. The past efforts involved enhancing NMDARs with co-agonists of NMDARs, such as glycine, D-serine and D-cycloserine, and indirectly with compounds which enhances the level of glycine by reducing their uptake (such as the inhibitor of glycine transporter-1). It has been found that agents that can enhance the function of NMDARs appear to exhibit certain beneficial effects in schizophrenia.
Methods: 1. in vivo calcium imaging by two photon microscope: we label the neuron in the frontal cortex with GCamP6s virus, and take a imaging in awake mice.

2. in vivo single unit recording: we place the microelectrode to the PFC, and record the neuronal activity.
Results: We found that in wild type mice, either glycine or D-cycloserine doesn't alter Ca2+ signals(N(mice)=5,5,5). However, in schizophrenia model mice with enhanced neuregulin 1 signaling, glycine significantly enhanced activity, putatively inhibitory neurons(N(mice)=3,3; $P<0.05$). We have also observed elevated activity in the neural network(N(mice)=5,6; $P<0.01$).
Conclusions: The results indicate a state-dependent contribution of glycine to neuronal spiking in vivo and therapeutic potential of NMDAR co-agonists in treating schizophrenia.
Supported By: Shenzhen government
Keywords: NMDAR Hypofunction, GABAergic Interneurons, Schizophrenia, NMDAR Co-Agonists

F253. Heterogeneity in Schizophrenia: Parsing by Temperament

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Background: Schizophrenia is a complex disorder with heterogeneous presentations. One possible source of heterogeneity is individual differences in temperament. Early differences in temperament have been associated with increased prevalence of multiple psychiatric disorders including anxiety and depression. The current study tested for an association between temperament and schizophrenia and examined the predictive validity of temperament on concurrent social and emotional functioning.
Methods: Participants were patients with schizophrenia ($N = 175$, 66.3% male) and healthy controls ($N = 186$, 58.6% male). Temperament was assessed by a validated self-report measure (Retrospective Self Report of Inhibition). Participants were classified as having inhibited, average, or uninhibited temperament based on cutoffs for standard, top, and bottom 15%. Concurrent measures included negative and positive symptoms of schizophrenia, anxiety and depression symptoms, personality, and quality of life. We tested for an association between temperament and diagnosis with a chi-square test and for associations between temperament and clinical features with an ANOVA.
Results: 32.6% of patients with schizophrenia had an inhibited temperament compared to 5.4% of healthy controls ($p < 0.01$). Within patients with schizophrenia, temperament predicted higher levels of anxiety and depressive symptoms, lower quality of life, lower extraversion, higher neuroticism, and higher schizotypal personality scores ($p < 0.01$ for all findings; partial eta squared ranged from 0.16-0.29).
Conclusions: The current study parsed the heterogeneity of patients with schizophrenia using temperament to explain variation in the social/emotion components of schizophrenia. These results suggest a novel neurodevelopmental pathway to schizophrenia characterized by temperament.
Supported By: Jack Martin Research Professorship (held by JUB)
Keywords: Schizophrenia, Temperament, Anxiety

F254. Social Processing Subtyping and Functional Neural Architecture Across Autism Spectrum Disorder, Schizophrenia and Non-Clinical Sample

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Background: Social processing includes complex social-emotional processes, e.g. social perception and cognition, on continua, with mental illnesses, e.g. autism spectrum disorder (ASD) and schizophrenia (SZ), hypothesized to be at one extreme. However, the nature of social dimensions and their relationships to different disorders is unclear. We characterized social phenotypes and subtypes across clinical and non-clinical populations and their relationships to neural function.
Methods: Sixty SZ, 42 ASD and 73 healthy controls (HC), ages 18-58 (M=26.1), completed a battery of social-emotional tests and resting state fMRI. Factor analysis (FA) was applied to 13 subscale measures and resulting factors entered into a two-step cluster analysis (CA) to identify associated phenotypic groups across all participants. Independent component

analysis and functional network connectivity identified connectivity patterns associated with phenotypic vs. diagnostic groups in the default mode (DMN), salience and executive networks.
Results: FA identified five social-emotional factors; although four showed significant group differences, factor loadings overlapped significantly between diagnostic groups. CA identified 3 clusters, not overlapping with diagnostic groups (group 1: N=78, 66.7% HC; 2: N=49, 44.9% ASD; 3: N=48, 64.6% SZ). These social-phenotypic (S-P) groups predicted social abilities measured by an observational tool (ADOS; F=19.6, $p<0.001$). Imaging analysis showed abnormal connectivity patterns unique to the phenotypic (vs. clinical) groups, e.g. only S-P group 3, characterized by high degree of daydreaming, showed significant DMN connectivity between OFC and precuneus ($p<0.01$).
Conclusions: Social subtypes, across ASD, SZ and HC revealed homogenous groups relevant to real-life social functioning and neural architecture, with further implications for individualized neural treatment targets.
Supported By: NIMH: R01 MH095888 (PI: M. Assaf); NARSAD: Young Investigator Award #17525 (PI: S. Corbera)
Keywords: Social Processing, Subtypes, Autism Spectrum Disorder, Schizophrenia, Functional Brain Connectivity

F255. Motivation System Impairment Profiles in Schizophrenia and Major Depressive Disorder

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Background: Amotivation is a prevalent symptom in schizophrenia (SZ) and major depressive disorder (MDD), and has been linked to poor functional outcomes. While current conceptualizations of motivation outline a multi-faceted system, previous studies have primarily focused on isolated facets typically within single illnesses. The present study sought to concurrently examine the multiple facets of motivation across SZ, MDD, and healthy control (HC) participants.
Methods: Thirty-nine SZ, 38 MDD, and 39 HC participants completed a series of clinical and cognitive assessments, as well as a battery of objective tasks to measure the discrete facets of motivation. Factor analysis was conducted to explore the structure of the motivation framework. Cluster analysis was subsequently used to classify individuals according to specific motivation deficits.
Results: Factor analysis revealed a five factor motivation system comprised of hedonic capacity, reward expectancy and learning, cost-benefit decision-making, goal-directed decision-making, and effort expenditure. Cluster analysis provided a two factor solution, with cluster 1 characterized by impairments in hedonic capacity ($t(114)=-3.7$, $p<.001$), and cluster 2 characterized by impaired cost-benefit decision-making ($t(114)=5.9$, $p<.001$), goal-directed decision-making ($t(114)=7.3$, $p<.001$), and effort expenditure ($t(114)=6.3$, $p<.001$). While clusters did not significantly differ by symptom severity, cluster 2 was significantly older ($t(114)=-5.7$, $p<.001$) and more cognitively impaired ($t(114)=6.4$, $p<.001$) compared to cluster 1.
Conclusions: Highlighting the heterogeneous presentation of amotivation, our results revealed two unique motivation impairment profiles with potentially distinct underlying neurobiological mechanisms. Dimensional investigations of the reward system may serve to improve specificity in characterizing motivation deficits across disorders, with opportunities to inform more targeted treatment interventions.
Supported By: OMHF
Keywords: Amotivation, Schizophrenia, Major Depressive Disorder (MDD), RDoC

F256. Changes in Morning Salivary Melatonin Correlate With Prefrontal Responses During Working Memory Performance

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Background: Humans demonstrate a circadian rhythm of melatonin production that closely tracks the daily light/dark cycle, with profound increases in circulating levels during the nighttime and nearly non-existent levels during daylight hours. While melatonin is known to play a role in preparing the brain and body for sleep, its effects on cognition and brain function are not well understood. We hypothesized that declines in morning melatonin would be associated with increased functional activation within cortical regions involved in alertness, attention, and behavioral control.
Methods: We measured the change in salivary melatonin from mid- to late-morning in 26 healthy young adults (13 female) who were also exposed to a 30-minute period of blue or amber light followed by functional magnetic resonance imaging (fMRI) during a working memory task (N-Back). Brain activation was regressed on change in melatonin scores and the role of light exposure was also assessed.
Results: Although overall melatonin levels did not change significantly over the morning at the group level, individual declines in salivary melatonin were associated with significant increases in activation within the left dorsomedial and right inferior lateral prefrontal cortex ($p < .05$, cluster corrected). Medial prefrontal activation also correlated modestly with better vigilance performance during the 0-Back ($p < .05$), but not the 1-Back or 2-Back conditions. Light condition did not affect the outcomes.
Conclusions: These findings suggest declining melatonin levels in the morning are associated with increased prefrontal cortex functioning, and may play a role in the increased frontal activation that occurs following awakening.
Supported By: USAMRMC (W81XWH-14-1-0571)
Keywords: Melatonin, Working Memory fMRI, Working Memory, Circadian Rhythms

F257. Pupillary Window to Assess Emotion- Somatization Connection: Alexithymia, Somatization and Pupillary Responses to Affective Stimuli

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Background: Somatoform disorders are associated with deficits in emotion processing. The neurophysiological correlates of this relationship are not well known. Pupillary responses provide information about arousal to affective information. Hence, we investigated the relationship between individual's tendency for somatization and affective processing through pupillary responses to affective images, emotion recognition, and alexithymia.
Methods: Forty college students filled surveys for modelling of somatization, current symptoms of depression, anxiety, dissociation and alexithymia, in addition to various measures of stress and resilience. Pupillary responses to affective images (neutral, fear, sadness, happiness, and disgust) were measured. Participants also completed the Emotion Recognition-40 task (ER40).
Results: Higher scores in alexithymia, dissociative experiences scale, and anxiety correlated with fewer correct responses to fear recognition ($p<.001$). In addition, alexithymia scores correlated with amplification of somatic symptoms ($p<.001$), attribution to physical disease ($p<.01$) and larger mean pupil diameter differences in early and late post image onset (MPDDinELPIO) of sadness ($p<.01$), whereas somatic dissociation questionnaire (SDQ) scores correlated with larger MPDDinELPIO of disgust ($p<.01$). Independent of stress, depression, anxiety, somatic attribution, emotion recognition, age, and gender, MPDDinELPIO of disgust was predicted by SDQ ($p<.01$); and MPDDinELPIO of sadness was predicted by both SDQ ($p<.01$) and alexithymia ($p<0.001$).
Conclusions: Our findings suggest that alexithymia and somatic dissociation are associated with increased somatic complaints and differentiated pupillary responses to some negative emotional stimuli. Assessment of pupillary responses to negative valence stimuli could be used to understand the neurophysiological correlates of somatization.
Keywords: Somatization, Pupil Dilatation, Psychophysiology, Emotion Recognition

F258. Negative Emotional Face Processing Associated With Alcohol Use Disorder Severity

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Background: In the United States, 13% of adults are estimated to have alcohol use disorder (AUD). Most studies examining the neurobiology of AUD treat individuals with this disorder as a homogeneous group; however, the neurocircuitry of AUD, which is theorized to be made up of three interconnected processes (bing/intoxication, withdrawal/negative affect, and preoccupation/anticipation), may hold the key to subtypes of AUD. Here, we aim to understand how AUD severity is associated with the withdrawal/negative affect circuit.
Methods: Adult men and women with moderate to heavy alcohol use ($N = 56$) were scanned on a 3T MRI machine while completing a Face Matching task. During this task, participants viewed a target picture and two additional pictures; participants were instructed to select the picture that matched the target by pressing the corresponding button. The pictures were made up of emotional faces, neutral faces, and shapes. We assessed AUD severity using the Alcohol Use Disorders Identification Test (AUDIT).
Results: During processing of negative emotional faces, there was a negative association between AUDIT score and neural activity in salience, default mode, and executive control networks. Specifically, the interaction between AUDIT and demographic variables was significant in the anterior/posterior cingulate, anterior insula, cerebellum, and superior frontal gyrus.
Conclusions: Negative emotional face processing, associated with the withdrawal/negative affect neurocircuit of addiction, was associated with less neural engagement across networks as AUD severity increased. Our results suggest that AUD severity beyond diagnostic threshold is associated with a biomarker of negative outcomes, suggesting clinical utility for this measure.
Supported By: NIAAA Intramural
Keywords: Alcohol Use Disorder, Emotional Face Processing, Brain Imaging, fMRI

F259. Social Motivational Processing and Interpersonal Function in Aging Cocaine Smokers

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Background: Illicit drug use among aging individuals is increasing, but little is known about its impact. Given the importance of social integration for aging, and documented social problems in cocaine users, we examined social function and its neurocognitive substrates in aging cocaine users relative to carefully matched non-cocaine users.
Methods: Regular ($\geq$ twice/week), long-term ($\geq$ 15 years) cocaine smokers, 50-60 years old (COC; $n = 22$; 4 females) and age-matched controls (CTRL; $n = 19$; 4 females) underwent standardized probes of social reward and threat processing during functional Magnetic Resonance Imaging and a behavioral facial affect recognition task. Self- and peer-reports of daily interpersonal function were also collected. COCs, and

CTRLs reporting current cannabis or alcohol use, were tested after 4 drug-free inpatient days.
Results: COCs had pronounced problems in daily social function relative to CTRLs as indicated by both self and peer reports ($p < 0.005$). Compared to CTRLs, COCs had stronger amygdala responses to social threat versus control stimuli ($p < 0.05$; small volume correction in amygdala ROI), with no other differences in social processing or cognition.
Conclusions: Aging cocaine users have generalized difficulties in 'real-world' interpersonal function but largely intact social processing on laboratory-based measures when tested under drug abstinent conditions and compared to appropriately matched controls. Daily social difficulties may be related to transient factors such as acute/residual drug effects or cocaine-related changes in health behaviors (e.g. disrupted sleep, poor diet). Findings suggest that interpersonal function may be a valid intervention target for aging cocaine users.
Supported By: NIDA DA030540 and DA034877
Keywords: Cocaine, Aging, Social Cognition, Social Functioning, Social Threat

F260. Alcohol Use Disorder Symptomatology is Related to Disrupted Reward Neuro-Circuitry Responsiveness in Adolescents

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Background: In 2014, 8.1% of adults in the US were diagnosed with a substance use disorder, including alcohol use disorder (AUD) and/or cannabis use disorder (CUD). Alcohol and/or cannabis use during adolescence is associated with increased risk of developing AUD and/or CUD during adulthood. Animal and neuroimaging studies have shown that AUD and CUD are related to dysfunction in reward processing neuro-circuitries. However, very few studies to date have directly examined differential effects of AUD versus CUD on reward processing in adolescents. This preliminary study uses a Monetary Incentive Delay (MID) task to investigate reward neurocircuitry dysfunction during reward outcomes in adolescents with a history of AUD and/or CUD symptomatology.
Methods: 150 youths aged 14-18 years recruited from a residential treatment facility and the surrounding community completed a MID task during fMRI scanning. AUD and CUD symptomatologies were assessed using the Alcohol Use Disorder Identification Test (AUDIT) and the Cannabis Use Disorder Identification Test (CUDIT).
Results: There was a negative relationship between AUDIT scores and BOLD response modulated by reward received during the outcome phase of the MID task in bilateral ventral striatum (r's=-.332–.345, p's<.001). However, there was no relationship between CUDIT scores and BOLD response modulated by reward value in ventral striatum.
Conclusions: These data suggest that impaired functioning of reward processing neuro-circuitry in adolescents is related to AUD symptomatology, but not CUD symptomatology. Future work should examine whether these altered neural responses are risk factors for AUD or outcomes of AUD in adolescents.
Supported By: Boys Town National Research Hospital, National Institute of All Mental Health
Keywords: Alcohol Use Disorder, FMRI, Reward, Adolescents

F261. Emotion Processing in Youth Presenting With Substance Use Problems

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Background: Substance use is highly prevalent among adolescents, and associated with adverse health, poorer social outcomes and substance use in adulthood. Extensive evidence links adult substance use to reduced emotion regulation and attenuated sensitivity to affective stimuli in brain regions important for emotion processing. However, this relationship is less well studied in adolescence. This is surprising, given that substance use during this critical developmental period will likely have a strong impact on the neural mechanisms underlying emotion processing.
Methods: 83 youths (14-18 years old) were recruited from a residential treatment facility and the surrounding community. Participants completed a gender discrimination task for faces displaying differing levels of fear or happiness. Alcohol and chemical use were assessed using the Alcohol Use Disorder Identification Test (AUDIT) and Chemical Use Disorder Identification Test (CUDIT). Reported alcohol and chemical substance consumption ranged from none at all to heavy, with 61% reporting some to heavy consumption.
Results: A repeated measures ANCOVA was conducted on the emotional intensity modulated BOLD responses for Emotion (Fear, Happy), using AUDIT, CUDIT, and AUDIT x CUDIT as covariates. Substance use was associated with aberrant fearful face intensity modulation in posterior cingulate, dorsolateral prefrontal cortex, and posterior parietal cortex.
Conclusions: These data suggest that substance use in youth does indeed impact the neural mechanisms underlying emotion processing. Given the critical role facial expressions play in social interactions, these early substance use induced impairments may be related to some of the later adverse effects associated with adolescent substance use.
Supported By: Boys Town National Research Hospital, National Institute of All Mental Health

Keywords: Substance Use, Emotion Processing, Adolescence

F262. Modeling Opioid Maintenance Therapy in Rats: Effect of Chronic Buprenorphine on Responding for Drug-Paired Discrete Cues in a Non-Drug Context, Context-Induced Reinstatement of Drug Seeking, and Reacquisition of Oxycodone Self-Administration

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Background: High relapse rates perpetuate prescription opioid addiction, which drives the current drug overdose epidemic in the US. Opioid agonist (buprenorphine, methadone) maintenance therapy is an effective treatment for prescription opioid relapse. Our goal is to establish an experimental procedure in rats trained to self-administer the prescription opioid oxycodone that will allow us to compare the efficacy of an established treatment (buprenorphine) with that of newer of opioid agonists currently developed for analgesia.
Methods: We trained rats to self-administer oxycodone (0.1 and 0.05 mg/kg/infusion; 7 days/dose, 6-h/d) in Context A; drug infusions were paired with a discrete tone-light compound cue. We then implanted osmotic minipumps (s.c.) containing vehicle or buprenorphine (6 mg/kg/d) and performed three relapse tests: (1) responding for drug-paired discrete cues under extinction conditions in a non-drug context (Context B), (2) context-induced reinstatement of oxycodone seeking in Context A after extinction of operant responding in Context B, and (3) reacquisition of oxycodone self-administration in Context A.
Results: Chronic buprenorphine inhibited responding reinforced by drug-paired discrete cues in Context B and reacquisition of oxycodone self-administration in Context A, but did not significantly decrease context-induced reinstatement of oxycodone seeking.
Conclusions: Chronic buprenorphine reduced oxycodone relapse provoked by exposure to oxycodone-associated discrete cues or oxycodone itself, but had a minimal effect on relapse provoked by exposure to contexts previously associated with drug self-administration. We currently establish a dose-response of chronic buprenorphine, and test the efficacy of the biased mu opioid receptor agonist TRV130 and the mixed mu/nociceptin receptor agonist BU08028 in our opioid maintenance/relapse procedure.
Keywords: Relapse, Self-administration, Opioid Use Disorder

F263. Social-Based Voluntary Abstinence Prevents the Emergence of Incubation of Drug Craving

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Background: We recently developed a rat model of incubation of drug craving after voluntary abstinence achieved by providing rats with a mutually exclusive choice between methamphetamine and palatable food for several weeks. Here we determined whether this incubation phenomenon would occur after a period of voluntary abstinence where the alternative reward is access to a social peer.
Methods: We first trained rats to lever-press for either access to a social peer (60-s, 2-h/day, 6 days) or palatable food (5 pellets) and then methamphetamine (0.1 mg/kg/infusion, 6-h/day, 12 days). We then assessed relapse to drug seeking after 1 and 15 abstinence days. Between tests, different groups of rats underwent either social-based voluntary abstinence (15 trials/day), food-based voluntary abstinence (15 trials/day), or homecage forced abstinence.
Results: As in our previous studies, non-reinforced responding on the methamphetamine-associated lever in the relapse tests was higher after 15 days of food-choice voluntary abstinence or forced abstinence (incubation of methamphetamine craving). More importantly, rats demonstrated a strong preference for the social peer over methamphetamine (social-based voluntary abstinence). Additionally, prior exposure to social-based voluntary abstinence prevented the emergence of incubation of methamphetamine craving (lever-presses during the relapse test were similar on test days 1 and 15).
Conclusions: Results show that exposure to social -based voluntary abstinence prevented the emergence of incubation of drug craving and demonstrate the critical role of social factors in drug relapse, as assessed in animal models. We are currently exploring brain mechanisms underlying the inhibitory effect of social-based voluntary abstinence on incubation of drug craving.
Supported By: NIDA/NIH
Keywords: Animal Models, Voluntary Abstinence, Social

F264. Incubation of Discriminative Stimulus-Induced Cocaine Craving

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[1]NIDA IRP / NIH

Background: Environmental stimuli paired with cocaine experience can provoke craving and relapse in humans, and elicit cocaine seeking in rats. Previous studies have shown that discrete cue- but not context-induced relapse to drug seeking progressive increases after withdrawal (incubation of drug craving). Here we developed a trial-based discriminative stimulus (DS+/DS-) procedure and tested whether the rat's response to a DS that predicts cocaine availability incubates after withdrawal.
Methods: We first trained rats to self-administer cocaine in the presence of a DS+ that signals cocaine availability (FR1 reinforcement schedule; 3-h continuous access; 0.75 mg/kg/infusion; 6 sessions) and then transitioned them to a

trial-based design (30 trials/session; 60-s lever availability/trial; multiple infusions available per trial; variable inter-trial interval; 2 sessions). Next, we introduced a DS- that signals the absence of cocaine and trained the rats to discriminate between the two DSs within the same session (60 trials/session; 30 each of DS+ and DS-; 2 sessions of 3-h/day) for 6-10 days. Once the rats showed stable discrimination, we repeatedly tested them for DS-induced relapse to cocaine seeking after 1, 21, 60, 120 and 200 days of abstinence.

Results: We observed reliable cocaine self-administration and discrimination in the trial-based procedure, and robust DS-induced relapse to cocaine seeking at all timepoints. Further, we observed incubation of DS-induced cocaine seeking during abstinence.

Conclusions: We have developed a trial-based procedure for studying incubation of DS-induced cocaine seeking. Future studies will investigate the role of DS-specific neuronal ensembles in mediating this new form of incubation of cocaine craving.

Supported By: NIDA IRP / NIH

Keywords: Cocaine Self-Administration, Incubation of Craving, Discriminative Stimuli, Neuronal Ensembles, Rat

F265. Voluntary Alcohol Consumption Alters Poly-ADP Ribose Polymerase Activity and Expression

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[1]Jesse Brown VA Medical Center

Background: Reduced BDNF and PPARγ expression have been implicated in Alcohol Use Disorder (AUD). Ethanol (EtOH) induces Poly ADP Ribose Polymerase (PARP) enzymatic activity and expression with profound effects on gene expression. Two important mechanisms whereby PARP silences gene expression is through the post-translational addition of PolyADP Ribose (PAR) groups to Peroxisome proliferator-activated receptor gamma (PPARγ) and Lysine demethylase 4D (KDM4D). KDM4D demethylates the transcriptionally repressive dimethylated histone H3 lysine 9 (H3K9me2) and PPARγ is a transcription factor, including for BDNF. The addition of PAR groups to PPARγ and KDM4D prevent them from interacting with DNA and increasing gene expression.

Methods: We allowed C57BL/6J mice to voluntarily consume alcohol in the binge-like drinking-in-the-dark (DID) paradigm (water bottles replaced with 20% ethanol for two hours per day three hours into the dark cycle for three consecutive days and four hours on the fourth day). Mice were injected with either vehicle or PARP inhibitor ABT-888 25 mg/kg i.p. just prior to EtOH exposure on the fourth day and sacrificed immediately after the final four hour drinking period.

Results: Our data indicate that binge-like EtOH consumption by C57BL/6J mice induced PARP expression in the NAc, VTA and PFC and enzymatic activity in the VTA and PFC. Binge-like EtOH consumption also decreased PFC PPARγ DNA binding ability and increased PFC H3K9me2 protein levels. The effect of EtOH on H3K9me2 was reversed by a PARP inhibitor.

Conclusions: Our results suggest that PARP may play a role in gene expression changes associated with binge-like alcohol consumption.

Supported By: This work was supported by the Veterans Affairs (Merit Review Grant Career Development Award (CDA-2) (IK2BX001650)) (D.P.G.).

Keywords: Alcohol Addiction, Epigenetic Biomarkers, Rewards Network, BDNF, Poly-ADP Ribose Polymerase

F266. Susceptibility to Traumatic Stress Accelerates the Development of Cocaine-Associated Dopamine Transients and Drives Cocaine Use Vulnerability

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Background: Post-traumatic stress disorder (PTSD) and cocaine use disorder are highly co-morbid psychiatric conditions, with PTSD onset generally occurring prior to the development of cocaine use disorder. Thus, it appears that development of PTSD drives cocaine use vulnerability, but the biological underpinnings of this vulnerability remain unresolved.

Methods: We recently characterized a model of PTSD using predator odor stress with segregation of subjects as susceptible or resilient based on elevated plus maze behavior and context avoidance. Using this model, paired with in vivo fast scan cyclic voltammetry in freely moving rats, we measured differences in phasic dopamine signaling (1) in response to a single injection of cocaine, (2) in response to repeated cues that predict the delivery of cocaine injections, and (3) in response to cocaine-paired cues in the absence of a cocaine delivery. In addition, we examined differences in the acquisition of cocaine self-administration behavior across groups.

Results: We found that susceptible subjects showed a heightened phasic dopamine response to a non-contingent injection of cocaine, and an increase in the rate at which cue-evoked dopamine transients developed over repeated cue to cocaine pairings when compared to resilient and control subjects. These neurochemical differences corresponded with an increase in cocaine self-administration acquisition in susceptible subjects relative to resilient and control subjects.

Conclusions: Together, our results suggest that the experience of traumatic stress increases the rate at which phasic dopamine signals entrain to cocaine-associated cues, and that this engenders vulnerability to developing cocaine use disorder following traumatic stress.

Supported By: NIDA R01DA031900 to R.A.E, and NIDA F31DA042505 to Z.D.B.

Keywords: PTSD - Posttraumatic Stress Disorder, Vulnerability to Cocaine Addiction, Dopaminergic Signalling, Self-administration, Systems Neuropharmacology

F267. Adenosine Signaling in the Neuron-Astrocyte Interaction and Alcohol Seeking Behaviors

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Background: Equilibrative nucleoside transporter 1 (ENT1) is an ethanol-sensitive adenosine transporter and regulates adenosine levels. Mice lacking ENT1 displayed elevated ethanol drinking with decreased ethanol sensitivity. Previously, we demonstrated that ENT1 deficiency dampens astrocyte function, which decreases adenosine A2A receptor (A2AR) function in the dorsomedial striatal (DMS) and increases ethanol-seeking goal-directed behavior.
Methods: We examined astrocyte-specific gene expression in mice lacking ENT1. Next, using dopamine receptor D2 (D2R) promoter-driven ENT1 overexpression virus, we investigated whether adenosine dynamics in D2R-expressing medium spiny neurons (D2-MSNs) of the striatum contribute to alcohol goal-directed behaviors.
Results: ENT1 ablation dampens glial fibrillary acidic protein (GFAP; astrocyte marker) and aldehyde dehydrogenase 1 family member A1 (ALDH1A1; dopaminergic axon terminal marker) in the striatum of naïve mice. Mice with increased goals toward alcohol displayed the reduction of GFAP, aquaporin-4 (AQP4), and c-Fos levels in the DMS. Viral D2R promoter-inducible ENT1 increases astrocytic glutamate transporter (GLT1) and A2AR mRNA levels in the DMS. In contrast to our initial hypothesis, ENT1 overexpression in the DMS D2R-expressing cells promotes alcohol-seeking behaviors and goal-directed behaviors. Viral-mediated DMS ENT1 overexpression increases ALDH1A1 and adenosine receptors in the DMS and dorsolateral striatum (DLS) but not GFAP and glutamate decarboxylase-65 (GAD65; GABAergic neuronal marker) after expression of ethanol goal-directed behaviors. Interestingly, DMS/DLS ALDH1A1 and DMS A1R have correlations with the expression of goal-directed behaviors, while DLS A2AR correlates with not goal-oriented behaviors but ethanol-seeking behaviors.
Conclusions: Our results demonstrate that striatal ENT1-regulated adenosine signaling plays an essential role in goal-directed and alcohol-seeking behaviors through for neuron-astrocyte interaction.
Supported By: R01AA018779, Samuel C. Johnson for Genomics of Addiction Program at Mayo Clinic, the Ulm Foundation, the Godby Foundation
Keywords: Alcoholism, Goal-Directed Behaviour, Optogenetics, Transporter, Astrocytes

F268. Transcriptional and Epigenetic Aspects of Incubation of Methamphetamine Craving

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Background: Substance use disorders are biopsychosocial problems defined as compulsive abuse of illicit substances despite adverse consequences. In the cases of psychostimulants, methamphetamine addiction is mimicked in rats that self-administer the drug. However, these self-administration (SA) models do not include adverse consequences that are necessary to reach a diagnosis of addiction in humans by the DSM. In addition, it is known that adverse consequences can impact the use of drugs differentially in individual subjects.
Methods: We trained rats to self-administer methamphetamine for 20 days and then we punish lever-presses for methamphetamine with mild footshocks of increasing intensity. Response-contingent punishment significantly reduced methamphetamine taking in some rats (shock-sensitive, SS) but not in others (shock-resistant, SR). Rats, receiving methamphetamine and footshocks were also yoked to rats that were receiving saline. Rats also underwent extinction test at one day and 30 days after the last shock session. Rats were euthanized one day after the second extinction test and brain tissues were collected to measure gene expression with microarray analysis.
Results: In the dorsal striatum, we found that 9 (6 up, 3 down) genes were affected in the SRvsSS comparison, including CARTpt that was upregulated. In addition, we observed that 9 (1 up, 8 down) transcripts were also affected in the nucleus accumbens, including oxytocin that was also upregulated. Quantitative PCR validated these results.
Conclusions: Accumbal oxytocin and striatal CARTpt may play important roles in the manifestation of incubation of methamphetamine craving in the rat. The epigenetic bases for these changes are presently being investigated.
Supported By: NIDA Intramural Research Program
Keywords: Methamphetamine Addiction, Microarray, Gene Expression, Oxytocin, Self-Administration

F269. Mitochondrial Transcriptome and Epigenetic Changes in the Human Hippocampus Chronically Exposed to Cocaine

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Background: In hippocampus, long-term adaptation requires gene expression changes. Several recent studies have shown that the functions of mitochondria are related to dendritic arborization and spine formation. Previous study found that oxidative phosphorylation related genes were differentially expressed in the hippocampus of chronic cocaine addicts. Here, we have performed a deeper analysis of the changes in expression of mitochondria associated genes and CircRNA to better understand the nature and origin of altered mitochondrial function in chronically cocaine addicts.
Methods: We profiled transcriptome changes in hippocampal region from chronically cocaine-exposed individuals, cocaine-addicts with excited-delirium status, and carefully matched

drug free control group. Eight chronic cocaine addicts, six cocaine addicts with excited delirium, and eight drug-free control subjects were selected for the study. Each hippocampal tissue sample was carefully matched for age, ethnicity, and postmortem interval and RNA quality was high as previously reported in detail.

Results: With differentially expressed genes in the chronic cocaine addicts and in the cocaine addicts with excited delirium, we subjected the differentially expressed genes to GO and pathway analysis to detect molecular and cellular functional domains impacted by chronic cocaine exposure. We observed a significant effect of long-term cocaine exposure on genes involved in mitochondrial functions and oxidative phosphorylation.

Conclusions: We observed gene expression changes and alternative splicing events that were related to decrease mitochondrial inner membrane functions, oxidative phosphorylation, and energy metabolism. These mitochondrial changes are also observed in neurodegenerative diseases. These results indicate this organelle may play an important role in long-lasting maladaptation occurring in the cocaine addiction.

Supported By: DA06227-18

Keywords: Cocaine Addiction, RNA-seq, Circular RNA, Human Postmortem Brain, Mitochondria

F270. Regularized Linear Regression Guides Development of a Multilocus Genetic Profile Score for Cannabis Use Disorder

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Background: The occurrence of cannabis use disorder (CUD) is approximately 10% in cannabis users, but will likely increase with cannabis legalization. Identifying risk factors for CUD and alleles that encode them may help quantify susceptibility in cannabis users. However, exploratory genetic analyses require large sample sizes to overcome the volume and complexity of genetic variability. Multilocus genetic profile (MLGP) scores infer the additive effect of multiple alleles, but these scores do not reflect allele interactions. Thus, our aim was to apply a machine learning method to identify risk alleles associated with CUD to develop a MLGP score using relatively small sample sizes and accounting for interactions between alleles.

Methods: We employed the least absolute shrinkage and selection operator (LASSO) technique on GWAS data from 235 cannabis users and assessed their cannabis use-related problems (Marijuana Problems Scale; MPS). A hypothesis-driven approach reduced the number of SNPs to only those with a previous association with CUD. The LASSO algorithm was optimized with MPS scores predictors for each SNP and interactions between SNPs as features.

Results: This method identified SNPs and allele interactions that contributed to the prediction of CUD severity. The number of risk alleles for each SNP correlated with MPS scores and subjective craving.

Conclusions: This method may reveal alleles and combinations thereof that contribute to CUD and benefit MLGP development to identify susceptible cannabis users. This will facilitate better diagnostic criteria for, and biological understanding of, CUD in conjunction with the goals of the Research Domain Criteria.

Supported By: R01DA030344

Keywords: Cannabis Use Disorder, GWAS, Machine Learning, Cannabis, Craving

F271. The Moderating Roles of Parental Monitoring and Peer Group Deviance on Polygenic Risk for Alcohol Use Across Adolescence

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[1]Virginia Commonwealth University, [2]QIMR Berghofer Medical Research Institute, [3]QIMR Berghofer Medical Research Institute, University of Queensland, [4]University of Amsterdam

Background: Twin studies have shown that parental monitoring (PM) and peer group deviance (PGD) moderate latent genetic variance in adolescent alcohol use (AU), but the effects of PM and PGD on aggregated, molecular genetic (i.e., polygenic) risk for AU within and across time remain unknown. The present study aims to examine whether polygenic risk predicts AU across late adolescence and if PM and PGD moderate the impact of polygenic risk.

Methods: We tested whether polygenic risk for AU predicts alcohol use at four ages (ages 16, 17, 18, and 20) in an independent sample using univariate linear regressions. We then tested whether PM and PGD moderated polygenic risk for AU at the four ages using multiple linear regressions with polygenic risk-by-environment interactions.

Results: Higher polygenic risk for AU predicted increased AU at age 20, but not at earlier ages. PM at age 12 moderated the impact of polygenic risk on AU at age 20, such that the association was attenuated under conditions of high PM. High PGD was associated with increased AU at all ages, whereas low PM was significantly associated with increased AU at age 16 only.

Conclusions: Given the moderating effect of early PM on polygenic risk for AU at age 20, the early risks associated with low PM, and the enduring risks of high PGD on AU, prevention and intervention efforts that focus on encouraging high levels of PM during early adolescence and decreasing exposure to PGD at all ages may reduce risk for alcohol misuse.

Supported By: UK Medical Research Council; Wellcome Trust; NIH R01

Keywords: ALSPAC, Alcohol Use, Polygenic Risk, Adolescence

F272. Psychiatric and Impulsivity Dimensions as Common and Specific Candidate Endophenotypes for Heroin and Amphetamine Dependence

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Background: Research reveals distinct psychiatric profiles and substance-specific manifestations of impulsivity among opiate and stimulant dependent individuals. However, findings have been inconclusive, due in part to the high rates of polysubstance dependence, which limit investigations of the common vs. specific effects of different drug classes. The aim of the present study is to examine sibling correlations on psychiatric symptoms and dimensions of impulsivity among individuals with 'pure' heroin and amphetamine dependence in Bulgaria, in order to explore their utility as common vs. specific endophenotypes for opiate and stimulant dependence.
Methods: Pearson correlations between individuals with heroin (N=34) and amphetamine (N=28) dependence and their non-dependent siblings were run on 5 externalizing, 7 internalizing, and 14 impulsivity (7 neurocognitive and 7 personality) measures.
Results: Among heroin sibling pairs, the following cross-trait correlations were significant: ADHD & Psychopathy; ADHD & Antisocial Personality Disorder; and Hopelessness & Alexithymia. The following within-trait correlations were significant: Hopelessness; Anxiety Sensitivity; Sensation Seeking; decision-making on the Cambridge Gambling Task, and risk taking on the Balloon Analogue Risk Task. Among amphetamine sibling pairs, there were significant cross-trait correlations between ADHD & Psychopathy and between State & Trait Anxiety; and significant within-trait correlations in Anxiety Sensitivity and response inhibition on the Go/No Go Task.
Conclusions: Different patterns of sibling correlations emerged, some of which were common and some of which were specific to heroin and amphetamine dependence. These results challenge the unitary account of drug addiction and may inform the development of substance-specific prevention and intervention programs for heroin and amphetamine dependence.
Supported By: R01DA021421 (to JV) by NIDA and Fogarty International Center
Keywords: Opiates, Stimulants, Impulsivity, Psychiatric Comorbidities, Endophenotype

F273. Plasma Soluble CD14 is Associated With Apathy in Adults With a History of Methamphetamine Dependence

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Background: Inflammation is a key mechanism of methamphetamine (MA)-induced neurotoxicity. Emerging evidence suggests that inflammation is also linked to apathy, a prevalent neuropsychiatric symptom in MA dependence that is associated with worse every day functioning. However, no study has examined whether inflammation is associated with increased apathy in the context of MA dependence. We examined the effect of MA dependence on apathy and associations between apathy and a panel of biomarkers indicative of inflammation (IL-6, sTNFR-II), chemotaxis (MCP-1, IP-10) and monocyte activation/microbial translocation (sCD14).
Methods: Excluding severe psychiatric or neurological disease, 75 adults with lifetime histories of MA dependence (MA+, n=24) and a non-drug-using comparison group (MA-, n=52) completed comprehensive neurobehavioral and neuromedical assessments, including measures of five plasma biomarkers by immunoassay. Apathy was measured using a composite of apathy-related subscales from the Frontal Systems Behavioral Scale, Profile of Mood States, and Beck Depression Inventory-II.
Results: Apathy was elevated in the MA+ group relative to MA- group ($p<.0001$), independent of potential confounds (e.g., education, Major Depressive Disorder). In the MA+ group, apathy was strongly associated with plasma sCD14 (rho=0.59, $p=.002$), while it was not associated with other biomarkers (ps>.05).
Conclusions: Results suggest that processes involved in monocyte activation, as reflected by sCD14, may contribute to apathy in MA dependence. sCD14 is typically triggered by bacterial lipopolysaccharide, and can be indicative of microbial translocation from the gut. Future work will determine if such translocation reflects MA-related microbiome changes, which in turn may affect gut-brain signaling, impacting affective behavior, such as apathy, relevant to MA dependence.
Supported By: T32-DA031098, P50-DA026306, R25-MH081482, K23-DA037793, P30-MH62512
Keywords: Apathy, Behavioral Biomarkers, Methamphetamine Dependence, Gut Microbiome, Inflammation

F274. Paired Associative Stimulation Influences Response Inhibition: Cortico-Cortical and Cortico-Subcortical Networks

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[1]University of Cambridge, [2]University College London

Background: The ability to stop a suboptimal response is integral to decision making and is commonly impaired across psychiatric disorders. Cortical paired associative stimulation (cPAS) is a form of transcranial magnetic stimulation in which paired pulses can induce plasticity at cortical synapses. PAS protocols have predominantly focused on the motor domain. Here we used cPAS protocols targeting cortico-cortical and cortico-subcortical networks by using different intervals of paired pulses to modify response inhibition in healthy controls.
Methods: Twenty-six healthy volunteers underwent 4 cPAS sessions in random order 1 week apart: right inferior frontal

cortex (rIFC) stimulation preceding pre-supplementary motor area (pre-SMA) stimulation by 10 or 4 milliseconds; pre-SMA stimulation preceding rIFC stimulation by 10 or 4 milliseconds. Subjects were tested on the stop signal task along with the delay discounting task as control at baseline, and after each cPAS session.

Results: The stop signal reaction time showed a main effect of PAS condition when controlling for age ($F(4,76) = 4.534$, $p = 0.002$). Younger subjects had greater impairments in response inhibition when the pre-SMA pulse preceded the rIFC pulse by 10 msec. In older individuals, response inhibition improved when the rIFC pulse preceded the pre-SMA pulse by 4 msec. There were no effects observed on delay discounting.

Conclusions: cPAS modified response inhibition through age-dependent plasticity mechanisms via putative cortico-cortical and cortico-subcortical networks. We show for the first time the capacity for cPAS to modify a cognitive process highly relevant to psychiatric disorders.

Supported By: Medical Research Council

Keywords: Transcranial Magnetic Stimulation, Response Inhibition, Plasticity, Age, Associative Learning

F275. Galantamine-Memantine Combination Targets Cognitive Impairments in Schizophrenia and Kynurenine Pathway Metabolites: A Battalion of Novel Biomarkers

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Background: Treatment for cognitive impairments associated with schizophrenia (CIAS) is a major clinically unmet need. The aim of this study was to examine whether the galantamine-memantine combination was effective for CIAS.

Methods: In this 6-week open-label clinical trial, three participants with schizophrenia were enrolled; two completed the study. Participants received galantamine ER 24 mg and memantine XR 21 mg for four weeks. Plasma was analyzed for kynurenine pathway (KP) metabolites.

Results: In a 36-year old male with schizophrenia, scores improved in five of seven MATRICS Consensus Cognitive Battery (MCCB) domains except working memory and verbal learning. In a 45-year old male with schizoaffective disorder, there were improvements in speed of processing and working memory. Picolinic acid (PIC) concentration decreased in both the participants. Kynurenic acid concentration decreased in both participants, and kynurenine concentration decreased in one participant.

Conclusions: This is the first study that suggests the association of MCCB and KP metabolites in schizophrenia. This is the first attempt to test whether there is synergy between cholinergic and glutamatergic systems and can be simultaneously targeted to treat cognitive deficits associated with schizophrenia. The decrease in PIC concentration with the treatment is a promising finding because high concentrations of PIC are toxic to the brain and can be explained by the NMDA antagonist action of memantine. KP metabolites are novel biomarkers to detect the severity of cognitive impairments and monitor the progress with treatment. This combination targets the triple hypotheses concurrently - nicotinic-cholinergic, glutamatergic/NMDA and kynurenic acid.

Supported By: Sheppard Pratt Health System, Baltimore, MD, USA

Keywords: Schizophrenia, Cognition, Kynurenine, Galantamine, Memantine

F276. Use of HIV Post-Exposure Prophylaxis Among Women Sexual Assault Survivors is Not Associated With Increased Posttraumatic Stress Symptoms

Arnav Singla[1], Jenyth Sullivan[1], Kristen Witkemper[1], Nathan Markiewitz[1], Heather Swain[1], Teresa D'Anza[2], Kathy Bell[3], Megan Lechner[4], Jennie Buchanan[5], Ix Chel Morrison[6], Rhiannon Reese[7], Jeffrey Ho[8], Gordon Reed[9], Ralph Riviello[10], Elizabeth Datner[11], Melissa Platt[12], Catherine Rossi[13], Patricia Nouhan[14], April Soward[1], and Samuel A. McLean[1]

[1]University of North Carolina at Chapel Hill, [2]Albuquerque SANE Collaborative, [3]Tulsa Forensic Nursing Services, [4]Memorial Health System, [5]Denver Health, [6]Austin SAFE, [7]University of Birmingham, [8]Hennepin County Medical Center SARS, [9]Christiana Care, [10]Philadelphia SARC, [11]Einstein Medical Center, [12]University of Louisville, [13]Cone Health System, [14]Wayne State University

Background: To reduce HIV risk, post-exposure prophylaxis (PEP) is prescribed to some women sexual assault (SA) survivors who present for emergency care after SA. However, the use of HIV PEP, and/or accompanying medication side effects, may serve as reminders of the SA, augmenting posttraumatic stress symptoms (PTSS).

Methods: Women $\geq$ 18 years of age presenting within 72 hours of SA to one of the 13 US sites in the Better Tomorrow Network were enrolled. Information regarding HIV PEP use was obtained from the medical record and confirmed via participant self-report. PTSS (PCL for DSM-IV) were evaluated at six-week follow-up.

Results: Among woman SA survivors enrolled to date ($n=422$), 287 had complete medical record data, concordance between self-report and medical record data regarding HIV PEP use (yes or no), and six-week follow-up data (80% of total sample). These women constituted the study sample. 46/287 (16%) women completed an HIV PEP regimen. Sociodemographic characteristics in women who did and did not receive HIV PEP were similar. In linear regression analyses adjusted for age and peritraumatic distress, receipt of HIV PEP was not associated with increased PTSS at six weeks ($F=0.82$, $p=0.441$). Receipt of HIV PEP was also not associated with worse depressive symptoms or mental health outcomes.

Conclusions: Receipt of HIV PEP is not associated with more severe posttraumatic stress symptom outcomes.

Supported By: R01AR064700

Keywords: HIV Post Exposure Prophylaxis, Posttraumatic Stress Symptoms, Sexual Assault, Better Tomorrow Network

Saturday, May 12, 2018

POSTER SESSION 3
5:00 p.m. - 7:00 p.m.

S1. Age-Associated Changes in Human Hippocampal Neurogenesis and Angiogenesis

Maura Boldrini[1], Laika Simeon-Thompson[2], Camille Fulmore[3], Alexandria Tartt[3], Andrew J. Dwork[3], Victoria Arango[3], Gorazd B. Rosoklija[4], Rene Hen[3], and J. John Mann[3]

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Background: Adult hippocampal neurogenesis (AHN) declines after middle age in rodents and primates. Smaller dentate gyrus (DG), less exercise-induced angiogenesis, and declining AHN are hypothesized in aging humans. However, age effects on human AHN, angiogenesis and DG volume have never been studied concurrently.
Methods: We studied 28 subjects, 14 to 79 years of age (11 females and 17 males), with postmortem interval 6-26 hours, from the Columbia Psychiatry/NYSPI Brain Collection. Using our validated psychological autopsy, we excluded subjects with neuropsychiatric diagnosis, positive toxicology, suicide attempts, and resuscitation with prolonged (>10min) hypoxia. Immunocytochemistry and immunofluorescence were performed on serial sections throughout the whole rostro-caudal extent of the DG. Confocal microscopy and stereology were used to assess and quantify cells single- and double-labeled for sex-determining region Y-box 2 (Sox2), polysialylated neural cell adhesion molecule (PSA-NCAM), Ki-67, nestin, doublecortin, and neuronal nuclei marker (NeuN). Tissue was stained with Nissl to identify nuclei and glial cells.
Results: In healthy human brain postmortem, we found no age-related changes in intermediate neural progenitors, immature and mature granule neurons, glial cells, and DG volume across 65 years of human lifespan. In contrast, angiogenesis and cells expressing Sox2 and PSA-NCAM declined with age selectively in anterior DG.
Conclusions: AHN persists into the eighth decade of life in people without cognitive impairment, neuropsychiatric disease or treatment, possibly sustaining human-specific complex cognitive functions during a long lifespan. Fading angiogenesis, stem cell pool and neuroplasticity may result from less exercise or higher stress and account for declining resilience, becoming possible targets to enhance healthy aging.
Supported By: Stroud Center for Aging Studies at Columbia University, NIH grants MH83862, MH64168, MH40210, NS090415, MH94888, MH090964, MH098786, American Foundation for Suicide Prevention Standard Research Grant SRG-0-129-12, Brain and Behavior Research Foundation Independent Investigator Grant 56388, New York Stem Cell Initiative (NYSTEM) C029157 and C023054, and the Diane Goldberg Foundation

Keywords: Neural Progenitor, Doublecortin, Dentate Gyrus, Nestin, Sox2

S2. A Robust Measure of Pathological Neuroinflammation in the Human Cortex

Daniel Felsky[1], Tina Roostaei[1], Julie Schneider[2], Kwangsik Nho[3], Andrew Saykin[3], David Bennett[2], and Philip De Jager[1]

[1]Columbia University Medical Center, [2]Rush Alzheimer's Disease Center, [3]Indiana Alzheimer's Disease Center

Background: Microglia are fundamentally important phagocytic brain cells vital for the maintenance of central nervous system homeostasis and its response to injury. However, little is known about the molecular-genetic causes or consequences of microglial activation in the aging human brain.
Methods: We analyzed the effects of microglial activation on human brain by calculating the square root proportion of active microglia (sPAM) in tissue sampled from four cortical and subcortical regions of 225 elderly subjects with comprehensive antemortem and postmortem neuropathological assessments. Microglia were marked by HLA antibodies, staged based on morphology, and counted manually.
Results: We found that cortical, rather than subcortical, sPAM strongly associated with amyloid and tau-related neuropathology, as well as the rate of longitudinal cognitive decline, at a magnitude comparable to and independent of APOE $\varepsilon 4$. Causal mediation analyses found that sPAM exerts its effects on cognitive decline indirectly via tau in consort with amyloid-beta. To uncover the genomic architecture of cortical sPAM, we performed two GWAS, discovering a genome-wide significant locus that also strongly impacted in vivo microglial activation measured by TSPO PET imaging in an independent sample. High resolution polygenic scoring on summary statistics from 22 published GWAS found overlap in genetic risk for high sPAM and other immune and aging-related traits, most notably AD.
Conclusions: In sum, we have developed and comprehensively characterized a novel score of microglial activation from postmortem brain that represents a large proportion of unexplained variance in AD-related neuropathology and cognitive decline.
Supported By: P30AG10161, R01AG15819, R01AG17917, R01AG30146, R01NS084965, Illinois Department of Public Health, Translational Genomics Institute, NIH
Keywords: Microglial Activation, Alzheimer's Disease, Human Postmortem Brain, PET Imaging, Polygenic Genetic Correlation

S3. Lithium Treatment Suppresses Intracellular Calcium Signaling and Blocks Nitrosative Stress and Tauopathy in the Hippocampus of 3xTg Alzheimer's Disease Model Mice

Seong Shim[1], Nicolas Kapecki[2], Clark Briggs[2], and Grace Stutzmann[2]

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Background: Although lithium is beneficial for Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE), the mechanism underlying its therapeutic potential is not well understood. To elucidate the mechanism, the effects of lithium on intracellular Ca2+ dysregulation, phosphorylated-tau, neuronal nitric oxide synthase (nNOS) and synaptic plasticity were determined in the hippocampus in 3xTg AD mouse model.
Methods: After feeding lithium diet to 3xTg AD and nonTg mice for one month, 2-photon Ca2+ imaging was used to determine the drug effects on inositol-3-phosphate (IP3)-gated Ca2+ release from endoplasmic reticulum and Ca2+ influx via voltage-gated calcium channel (VGCC) in CA1 pyramidal neurons. Postsynaptic potential at CA1-CA3 synapse was recorded to determine the drug effects on synaptic plasticity. Immunohistochemical stainings were used to determine the drug effects on regulation of nNOS and phospho-tau in the hippocampus.
Results: IP3-evoked Ca2+ release ($n=20$, $p<0.01$) and levels of phospho-tau ($n=40$, <0.0001) and nNOS ($n=24$, <0.0001) were elevated in 3xTg-AD neurons, not nonTg neurons. Lithium treatment significantly reduced IP3-Ca2+ release ($n=18$, $p<0.05$) and density of phospho-tau ($n=19$, $P<0.01$) and nNOS ($n=42$, $p<0.0005$) only in 3xTg neurons, not NonTg neurons. Lithium treatment reduced Ca2+ influx via VGCC ($n=18$, $p<0.005$) in 3xTg-AD neurons, not nonTg neurons. Lithium treatment increased post-tetanic potentiation, synaptic plasticity reliant on calcium signaling, in NonTg mice ($n=15$, $p<0.05$), not 3x Tg mice.
Conclusions: Lithium restores the normal regulation of Ca2+ signaling, leading to blockade of neurotoxic nitrosative stress and tauopathy. These molecular effects of lithium are likely to be an important therapeutic mechanism of lithium for AD and CTE.
Supported By: VA Merit grant
Keywords: Lithium, Calcium Signaling, Nitrosative Stress, Tauopathy, Alzheimer's Disease

S4. Influence of Δ9-Tetrahydrocannabinol (THC) on Fear Extinction Learning and Spontaneous Recovery

Mira Hammoud[1], Stephanie Gorka[1], Christine Rabinak[2], Israel Liberzon[3], Stephen Maren[4], K. Luan Phan[1], and Mohammed Milad[1]

[1]University of Illinois at Chicago, [2]Wayne State University, [3]University of Michigan, [4]Texas A&M University

Background: Preclinical and clinical studies suggest that Δ9-tetrahydrocannabinol (THC) facilitates fear extinction. The long-term effects of THC on fear and the neural mechanisms by which THC exert its effect in humans are unknown. We studied how THC might influence the expression of fear extinction, short and long-term spontaneous recovery (SR) in healthy subjects using functional MRI.
Methods: 40 individuals (24 women) underwent a 4-day fear-conditioning and extinction paradigm. Participants were randomized to take THC (dronabinol 7.5mg) or PBO 2 hours before extinction learning. Outcome measures were skin conductance and blood oxygenation level-dependent signal.
Results: During extinction learning, subjects in the THC group expressed blunted fear conditioned responses to the cues being extinguished. During short-term SR, the THC group expressed less conditioned fear than the PBO group ($p=0.055$). Neurobiologically, during extinction, the THC group showed greater activation in the vmPFC ($t=3.38$, $p=0.001$) and hippocampus ($t=3.69$, $p<0.0001$) compared to PBO. During SR, PBO group had higher activation of the vmPFC in the short-term ($t=3.17$, $p=0.002$) and long-term ($t=3.86$; $t=3.51$, $p<0.0001$) test intervals, and higher dACC during the short-term interval only ($t=3.44$, $p=0.001$). Lastly, we found that dACC and insula activations during extinction learning were negatively predictive of extinction recall level during the SR phase ($r=-0.49$ and $r=-0.38$, respectively).
Conclusions: THC appears to have an anxiolytic effect during extinction learning and reduction of spontaneous recovery during extinction recall. These data reveal mechanistic insight into how THC might influence the fear extinction and neural correlates of spontaneous recovery in healthy humans.
Supported By: R21
Keywords: Extinction Memory, Fear Conditioning, Fear and Anxiety, Skin Conductance, fMRI

S5. Percentage Rapid Eye Movement (REM) Sleep is Inversely Correlated With Percentage Light (N1+N2) Sleep in Posttraumatic Stress Disorder (PTSD)

Madhulika Gupta[1] and Daiana Pur[1]

[1]University of Western Ontario

Background: Fear conditioning in PTSD usually occurs in the context of a high sympathetic tone. A recent study has suggested that high baseline levels of REM sleep may protect against excessive activity in fear-related neural circuitry and fear conditioning (Lerner, 2017). REM sleep is typically associated with a high parasympathetic tone and a low sympathetic tone (in tonic REM). We examined the relationship of %REM with sleep physiological indices of arousal and a higher sympathetic tone during sleep e.g., %Light (stages N1+N2) sleep, to examine the possible role of %REM sleep as a biomarker of resilience in PTSD.
Methods: 40 consenting civilians with PTSD (38 female, mean±SD age: 44.60±12.73) underwent ≥1 nights of Level 3 home sleep testing (WatchPAT200; Itamar Medical, Israel) and completed a battery of instruments as part of a larger study of psychosomatic factors in PTSD.
Results: Data from the second night of sleep recordings are presented: the overall mean±SD %REM was 22.77±7.37%; %REM correlated with some of the sleep indices as follows: % light sleep (stages N1+N2):$r=-0.909$, $p<0.001$; sleep efficiency: $r=0.521$, $p=0.001$; no. awakenings/ hour: $r=-0.298$, $p=0.066$; sleep latency ($r=-0.483$, $p=0.002$); and REM latency ($r=-0.567$, $p<0.001$).
Conclusions: Percentage REM sleep was strongly negatively correlated with some indices of a relatively higher sympathetic tone and/or arousal during sleep eg., %light sleep. This previously unreported finding supports the position that higher % REM may be a biomarker for a low sympathetic tone and more consolidated and deeper sleep in PTSD, factors which can all

contribute to fear extinction and greater resilience in PTSD patients.
Keywords: PTSD - Posttraumatic Stress Disorder, Resilience, Parasympathetic-Sympathetic Balance, REM Sleep, Non-Rapid Eye Movement Sleep

S6. Fear of Sleep (FS) in Posttraumatic Stress Disorder (PTSD) Patients Correlates Directly With Indices of Hyperarousal During Wakefulness and Sleep

Madhulika Gupta[1] and Angelica Sheridan[1]

[1]University of Western Ontario

Background: Fear of sleep (FS) can be a significant factor in the sleep disturbances encountered in PTSD. We examined some psychologic and sleep physiologic correlates of FS.
Methods: 40 consenting civilians with PTSD (38 female, mean±SD age: 44.60±12.73) underwent ≥1 nights of Level 3 home sleep testing (WatchPAT200; Itamar Medical, Israel) and completed a battery of instruments including the Fear of Sleep Inventory (FOSI)) (Zayfert et al., 2006), a 23-item instrument where participants rate trauma-related sleep disturbances involving fear of sleep, Insomnia Severity Index (ISI) and PTSD Checklist for DSM-5 (PCL-5).
Results: The mean±SD PCL-5 score was 40.40±18.81. FOSI scores were directly correlated with total PCL-5 (Pearson $r=0.639$, $p<0.001$) score and its symptom subscales of Cluster B(intrusive symptoms) ($r=0.605$, $p<0.001$), Cluster C (avoidance) ($r=0.577$, $p<0.001$), Cluster D(negative cognitions) ($r=0.493$, $p=0.002$) and Cluster E(hyperarousal) ($r=0.654$, $p<0.001$), and the ISI ($r=0.548$, $p<0.001$). Multiple regression analysis using FOSI score as dependent variable and all PCL5 subscales and ISI as independent variables, revealed that only PCL-5 Cluster E ($\beta=0.648$, $t=4.959$, $p<0.001$) remained a significant predictor of FOSL (adjusted $R2=0.403$). The FOSI score correlated with sleep latency ($r=0.620$, $p<0.001$), mean pulse rate during sleep ($r=0.492$, $p=0.004$), sleep efficiency ($r=-0.547$, $p=0.001$), no. wakenings/hour ($r=0.353$, $p=0.044$), respiratory disturbance index ($r=0.480$, $p=0.003$) and oxygen desaturation index ($r=0.593$, $p<0.001$).
Conclusions: FS may be an index of the underlying drive for vigilance and sympathetic activation in PTSD patients. The previously unreported finding of a direct correlation of FS with indices of sleep-disordered breathing and heart rate during sleep, in addition to other measures of sleep fragmentation, further supports this.
Keywords: PTSD - Posttraumatic Stress Disorder, Hypervigilance, Hyperarousal, Parasympathetic-Sympathetic Balance, Insomnia

S7. Experimentally Assessing Costly Fearful Avoidance and its Relation to Anxious Psychophysiology

Floris Klumpers[1], Anneloes Hulsman[1], Reinoud Kaldewaij[1], Mahur Hashemi[1], Wei Zhang[1], Saskia Koch[1], Bernd Figner[1], and Karin Roelofs[1]

[1]Radboud University Nijmegen

Background: Avoidance behaviour is a critical maintaining factor for anxiety that often involves choosing short term safety rather than long term reward. Most studies into the psychophysiology of anxiety have focused on passive viewing of threatening stimuli without reward processing, unable to fully model the approach/avoid trade-off involved in avoidance.
Methods: We developed a paradigm allowing subjects to actively approach versus avoid threat of electric shock. A 50% chance of a rewarding outcome (monetary gain) was included to motivate approach. Threat versus no-threat trials were systematically varied with two levels of reward (high, low). Startle eye-blink was recorded to probe fear psychophysiology during decisions.
Results: In two independent healthy participant samples, this paradigm successfully induced approach-avoid conflict as reflected in behavioural outcomes (N=24/171). Specifically, avoidance increased during threat (vs. no threat; both samples p's <.001) yet was less frequent in high versus low reward (p's <.001). Startle eye-blink amplitude was found to be potentiated during the decisions under threat (p's <.05). Females showed enhanced costly avoidance compared to males (p <.05 − only tested in study 2), but no difference in startle. Finally, potentiated startle during decisions without threat indicative of fear generalization was associated with increased threat avoidance during high reward (p's <.05).
Conclusions: Sex differences in costly avoidance behaviour appear independent of threat appraisal (indexed by eye-blink startle) suggesting that reward-related processing might be important for further understanding individual differences in costly avoidance behaviour. Further, costly threat avoidance may share a common mechanism with generalization of psychophysiological fear responding to non-threatening situations.
Keywords: Anxiety, Approach/Avoidance, Fear-Potentiated Startle Reflex, Fear, Reward

S8. Influence of Behavioral Inhibition and EEG Resting State on Social Anxiety Symptoms

Anita Harrewijn[1], George A. Buzzell[1], Ranjan Debnath[1], Daniel S. Pine[2], and Nathan A. Fox[1]

[1]University of Maryland, [2]National Institute of Mental Health, National Institutes of Health

Background: Behavioral inhibition (BI) is an early temperamental style characterized by inhibition towards novel stimuli. Children with high BI have a higher risk of developing social anxiety disorder later in life. Longitudinal studies are needed to investigate which factors increase the risk for social anxiety in children with high BI. Possible biological factors are frontal alpha asymmetry and delta-beta correlation, which have both been studied in relation to (social) anxiety in children and adults. The goal of the present study is to examine the effects of BI, these EEG resting state measures, and their interaction on social anxiety.
Methods: We included 102 children (54 girls) whose BI was assessed at age 2 and 3 using behavioral observations and parental report. When these children were 12 years old, their EEG was measured during resting state (eyes closed), and their

social anxiety symptoms were measured using a questionnaire (SCARED). EEG analyses focused on relative frontal alpha asymmetry, and relative frontal delta-beta correlation.
Results: BI at age 2/3 predicts social anxiety at age 12, $\beta = 0.39$, $p = 0.023$. Alpha asymmetry and left delta-beta correlation were not related to BI, nor to social anxiety. Right delta-beta correlation marginally predicted social anxiety, $\beta = 4.53$, $p = 0.065$, and showed a marginal interaction with BI, $\beta = 0.31$, $p = 0.072$.
Conclusions: EEG during resting state does not seem a strong predictor of social anxiety. Delta-beta correlation might be related to increased social anxiety, but this effect could be clearer during state anxiety.
Supported By: NIMH
Keywords: Behavioral Inhibition, Frontal EEG Asymmetry, Social Anxiety, Delta-Beta Correlation

S9. Dynamic Salience Updating and its Role in Fear Acquisition and Extinction in PTSD

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Background: Posttraumatic stress disorder (PTSD) is associated with faster acquisition of fear responding to conditioned stimuli as well as impaired fear extinction. However, computational models clarifying mechanisms of learning have not been applied to fear learning and extinction in PTSD. The purpose of this study was to investigate altered fear learning and extinction in PTSD using models of reinforcement learning (RL).
Methods: Adult women with a current diagnosis of PTSD (N=44) completed a fear acquisition and extinction task during fMRI while collecting skin conductance response (SCR) data. Four variations of RL models were compared in order to understand fear learning in PTSD from a computational perspective.
Results: We found a hybrid RW model that dynamically updates salience in response to positive and negative prediction errors provided best fit to the data. Traditional contrast-based measures of SCR and PTSD symptom severity were related to individual differences in dynamic salience updating in response to positive and negative prediction errors (PE). We found that dynamic salience updating was encoded within striatum, cingulate and insula functional networks based on independent component analyses. Salience encoding within the striatum positively predicted degree of striatum activation during extinction and scaled positively with PTSD symptoms.
Conclusions: These data suggest that altered fear acquisition and extinction in PTSD may be partially due to alterations in dynamic salience updating and the encoding of salience in the striatum. Future research should investigate fear learning and extinction recall in PTSD to understand the longer-term implications of differential PE weighting.
Supported By: NIMH
Keywords: PTSD, Fear Extinction, Salience

S10. Automated Measurement of Hippocampal Subfields in PTSD: Evidence for Smaller Dentate Gyrus Volume

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Background: Smaller hippocampal volume has been consistently observed as a biomarker of posttraumatic stress disorder (PTSD). However, less is known about individual volumes of the subfields composing the hippocampus such as the dentate gyrus and cornu ammonis (CA) fields 1-4 in PTSD. The aim of the present study was to examine the hypothesis that volume of the dentate gyrus, a region putatively involved in distinctive encoding of similar events, is smaller in individuals with PTSD versus trauma-exposed controls.
Methods: Ninety-seven recent war veterans underwent structural imaging on a 3T scanner and were assessed for PTSD using the Clinician-Administered PTSD Scale. The hippocampal subfield automated segmentation program available through FreeSurfer was used to segment the CA4/dentate gyrus, CA1, CA2/3, presubiculum, and subiculum of the hippocampus.
Results: Results of hierarchical logistic regression showed that CA4/dentate gyrus subfield volume was significantly smaller in veterans with PTSD ($p = 0.009$) and scaled inversely with PTSD symptom severity ($p = 0.007$).
Conclusions: These results support the view that dentate gyrus abnormalities are associated with symptoms of PTSD, although additional evidence is necessary to determine whether these abnormalities underlie fear generalization and other memory alterations in PTSD.
Supported By: VA Rehabilitation Research and Development
Keywords: Dentate Gyrus, Hippocampus, PTSD - Posttraumatic Stress Disorder, Structural MRI, FreeSurfer

S11. Neural Mechanisms of Contextual Threat Learning in Clinical Anxiety: Discrimination and Regulation

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Background: Learning about dangers in our environment and predicting their occurrence is a vital adaptive behavior for survival. However, individuals with anxiety disorders exhibit dysregulation of this learning process, leading to anxiety symptoms. Little is known about how neural mechanisms of context conditioning learning are perturbed in anxiety patients. The present fMRI study aims to understand the neural mechanisms underlying contextual threat learning within a context and how these are perturbed in individuals with anxiety disorders.
Methods: Brain activity was recorded in healthy controls (HC; n= 20) and patients with generalized anxiety disorder (GAD;

n= 20), while performing a virtual reality task designed to generate threat context conditioning using an environment divided in two zones. Participants picked flowers appearing pseudo-randomly across the whole environment, and learned that only one zone was associated with threat of shock.
Results: Results show that both groups can learn to discriminate between safe and danger. However, GAD exhibit an enhanced skin conductance response even in safe zones. Approach to flowers in either zone was associated with higher activation in the dorsomedial prefrontal cortex and anterior insula, and a hypo-recruitment of the ventromedial prefrontal and posterior cingulate cortex. In addition, the period following the picking of flowers further activated the periaqueductal gray region and hypo-recruited the anterior hippocampus in GAD.
Conclusions: The present findings identify a network of regions that seem to contribute to learning about location-specific threats. This identified network might be vulnerable to emotional responses and be disrupted in anxiety disorders.
Supported By: NIMH T32 MH015144
Keywords: Anxiety Disorder, fMRI, Location-Specific Threat Conditioning, Context Conditioning, Learning

S12. Intrinsic Functional and Structural Connectivity of Emotion Regulation Networks in Obsessive-Compulsive Disorder

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Background: Emotion regulation, underpinned by the ability of the fronto-parietal network to regulate limbic regions, is altered in patients with Obsessive-Compulsive Disorder (OCD). We aimed to compare cortico-limbic functional and structural connectivity between OCD patients and healthy controls (HC), and to correlate this with the dispositional use of expressive suppression and cognitive reappraisal strategies.
Methods: Subject-specific left (LA) and right amygdala (RA) masks were extracted and connectivity maps were generated from them.

We first identified between-group differences in LA and RA whole-brain connectivity, and also evaluated the moderating effect of reappraisal and suppression scores (as assessed with the Emotion Regulation Questionnaire). Significant regions from the above analyses and amygdale seeds were used as regions of interest in probabilistic tractography analysis.
Results: OCD patients (n=73) scored significantly higher in suppression, while HC (n=42) scored higher in reappraisal.

We observed higher connectivity in HC compared to patients between the RA and the right post-central gyrus, and in patients these connectivity scores were correlated with the Y-BOCS. Higher reappraisal scores were associated with higher negative correlations between LA and left posterior insula specifically in HC. Conversely, we observed a negative association between suppression scores and LA – precuneus and angular gyri connectivity in OCD.

At the structural level, OCD patients showed higher diffusivity in the tracts connecting the amygdale with regions derived from functional connectivity results.
Conclusions: OCD patients showed altered connectivity between the amygdala and posterior regions of the emotion regulation network, both at the functional and the structural level, which were associated with suppression strategies.
Supported By: PI13/01958 and PI16/00889 (ISCIII); FEDER funds, a way to build Europe.
Keywords: Multimodal Neuroimaging, Obsessive Compulsive Disorder (OCD), Emotion Regulation, Functional Connectivity, Tractography

S13. Can Psychological Treatment Slow Down Cellular Aging in Social Anxiety Disorder? An Intervention Study Evaluating Changes in Telomere Length and Telomerase Activity

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Background: Mental illness, including anxiety disorders, is linked to accelerated cell aging. This is evidenced by shorter leukocyte telomere length. Cells with critically short telomeres may undergo apoptosis. In dividing cells, telomere shortening is counteracted by the telomerase enzyme. Telomerase is reportedly low following chronic psychological stress. We hypothesized that a psychological treatment may increase telomerase activity, less telomere attrition and greater symptom improvement.
Methods: Forty-six patients (91% SSRI naïve) with social anxiety disorder (SAD; mean age 31, 63% females) underwent a 9-week waiting period, and 9 weeks of Internet-delivered cognitive behavior therapy (CBT). During treatment, symptoms were assessed weekly using the Liebowitz Social Anxiety Scale (LSAS-SR). Fasting blood samples were collected twice before treatment, and at post-treatment. Genomic DNA was extracted using DNeasy® Blood & Tissue Kit (Qiagene) to assess leukocyte telomere length. Telomerase activity was detected by real-time telomeric repeat amplification protocol (RT-TRAP).
Results: Patients improved significantly on the LSAS-SR ($p<.001$; Cohen's $d=1.5$). Pre-post changes in telomerase and telomere length correlated positively (Pearson's $r=.31$, $p=.05$). Reduced telomerase activity (<33th percentile) was associated with less improvement and increased activity (>66th percentile) with more improvement on the LSAS-SR ($Z=-2.4$, $p=.02$).
Conclusions: We demonstrate, to our knowledge for the first time, that altered telomerase activity is associated with clinical response to a psychological treatment in a psychiatric population. The observed CBT effect on telomerase in patients with

SAD is consistent with results from animal trials and a small previous study of antidepressants in humans. Thus, telomerase activation may play an important role in clinical recovery.
Keywords: Telomerase, Telomere, Social Anxiety Disorder, Cognitive Behavior Therapy, Cellular Aging

S14. Randomized Controlled Trial of Hydrocortisone and D-Cycloserine on Fear Extinction in PTSD

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Background: Pharmacological augmentation of fear extinction has the potential to improve upon exposure-based treatments for PTSD. Cortisol is a stress hormone that modulates learning and memory and is altered in PTSD. D-Cycloserine (DCS) is an N-methyl-D-aspartate (NMDA) receptor partial agonist that has been shown to enhance fear extinction in animals and a helpful adjunct to exposure therapy in phobic patients. We examined whether Hydrocortisone or DCS enhances fear extinction in individuals with PTSD.
Methods: Using a double-blind placebo-controlled experimental design, 88 participants with PTSD underwent a fear conditioning task, in which they were exposed to computer-generated colored circles that were paired (CS+) or unpaired (CS-) with an aversive electrical stimulus (US). After 72 hours, randomly assigned participants received Hydrocortisone (25mg), DCS (50mg) or placebo one hour prior to extinction. Extinction recall was tested one week later. Skin conductance responses (SCR) served as the dependent variable.
Results: Mixed model analyses indicated that at the end of extinction, participants in the Placebo group showed greater CS+/CS- SCR differentiation compared to the DCS (b=-.13, p=.015) and Hydrocortisone groups (b=-.12, p=.023). During retention, participants in the Placebo group showed greater CS+/CS- SCR differentiation compared to the DCS (b=-.18, p=.008) and Hydrocortisone groups (b=-.16, p=.013).
Conclusions: These findings suggest that a single dose of Hydrocortisone and DCS facilitated SCR fear extinction learning and retention compared to placebo in individuals with PTSD. While the therapeutic efficacy of these drugs has yet to be determined, it is possible that these drugs may be useful in augmenting exposure treatment for PTSD.
Supported By: VA
Keywords: PTSD - Posttraumatic Stress Disorder, Fear Conditioning and Extinction, Hydrocortisone, D-Cycloserine

S15. Efficacy of Anodal Pre-Supplementary Motor Area Transcranial Direct Current Stimulation for Treatment Resistant Obsessive Compulsive Disorder: A Randomized, Double Blinded, Sham Controlled Study

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Background: Selective serotonin reuptake inhibitors (SSRI) and cognitive behaviour therapy (CBT) are the first-line treatments for obsessive compulsive disorder (OCD). However, a sizeable proportion of patients does not respond or only partially respond to the conventional treatment options. In this study, we examined the efficacy of add-on anodal pre-supplementary motor area(pre-SMA) transcranial direct current stimulation(tDCS) using a randomized double blinded, sham controlled design.
Methods: Effect of add-on tDCS [anode corresponding to left pre-SMA and cathode to right supra-orbital area;2-mA, twice-daily sessions for 5-days] to treat SSRI non-responsive OCD patients(N=25) was examined using a randomised sham controlled double-blind design. Following the RCT phase, patients who had less than 35% reduction in YBOCS severity were offered an open-label extension (OLE) active stimulation to evaluate the effect of cross-over to verum tDCS.
Results: In the RCT phase, repeated measures ANOVA with tDCS type [verum(N=12) vs. sham(N=13)] as between subjects factor demonstrated a significant tDCS-type X time-point interaction [$F(1,22)=4.95$,$p=0.04$,partial-$\eta 2=0.18$] with significantly greater reduction of AVH score in verum tDCS group as compared to sham group. Among those who received verum tDCS in RCT phase, there was a significant difference in the percentage reduction of YBOCS total score between the RCT phase and OLE phase($t=2.67$; $p=0.04$).
Conclusions: To the best of our knowledge, this is the first report of a sham-controlled double blind RCT of add-on tDCS for treatment resistant OCD and it demonstrates the efficacy and safety of anodal pre-SMA stimulation.
Supported By: Wellcome trust DBT India Alliance intermediate fellowship grant
Keywords: Obsessive Compulsive Disorder (OCD), Transcranial Direct Current Stimulation, Pre-Supplementary Motor Area

S16. The Effects of Oxytocin on Comorbid Symptoms of Posttraumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD): An Examination of Alcohol Craving, Social Perception, and Fear Potentiated Startle

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Background: Existing treatments for individuals with comorbid PTSD and AUD are limited and inadequate. We aim to determine whether administration of intranasal oxytocin has beneficial anti-addiction, social, and hyperarousal-reducing effects in patients with PTSD/AUD. Differential effectiveness of

high (40IU) versus low (20IU) dosages of oxytocin and predictors for individual responsiveness will be examined.
Methods: Patients meet DSM-5 criteria for PTSD and AUD. Participants undergo a laboratory-based, randomized, placebo-controlled, dose-tiered (placebo, 20IU and 40IU), within-subject design with three testing days separated by at least one week. At each session, thirty minutes after drug administration, participants complete a cue-induced alcohol craving task, a FaceMorph Task (measures perception of emotion in animated morphed faces), and a fear-potentiated startle task.
Results: 42 patients and 37 controls have completed the study to date; we remain blinded to drug condition in this ongoing study. Preliminary data analysis demonstrates patients, but not controls, demonstrate significantly higher alcohol craving after exposure to alcohol, using visual analog scales 0-100 Mean (SD): PTSD: 58.9 (33.2) HC:7.6(19), compared to water, PTSD:33.5(31.2)/HC:12.2(21.9). Patients demonstrate increased latency ($p=0.04$) and decreased accuracy ($p=0.05$) when discerning fear, anger, and joy in the FaceMorph Task, with the most difficulty accurately identifying anger (PTSD:0.74(0.20), HC:0.89(0.12)).
Conclusions: This study will inform a future longitudinal clinical trial of chronic oxytocin administration to treat comorbid AUD and PTSD symptoms. While we remain blinded to drug condition, our results indicate that our paradigms adequately detect differences between groups. Data collection will complete 12/2017. Complete results will be presented.
Supported By: Defense Health Program in the Department of Defense; Institute for Translational Neuroscience, UCSF
Keywords: Oxytocin, Post Traumatic Stress Disorder, Alcohol Use Disorder, Psychophysiology, Anxiety

S17. Resting State Functional Connectivity in the Default Mode Network (DMN) in Patients With Maladaptive Self-Focused Attention

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Background: Maladaptive self-focused attention is a bias toward internal thoughts, feelings, beliefs, and physical states, and may reflect a mechanism underlying many psychiatric disorders. In this study, we use resting state functional connectivity to investigate whether patients with maladaptive self-focus demonstrate increased connectivity of the DMN, compared to controls, and whether connectivity correlates with more psychopathology.
Methods: To date, eight participants have completed the protocol: six patients with maladaptive self-focus and two healthy controls. Eligibility was determined by scoring one standard deviation above or below the sex-specific normative means on the Public Self-Consciousness Scale, respectively for each group. Participants completed a six-minute resting state scan. Connectivity analyses were conducted in the CONN Toolbox (www.conn-toolbox.org) using standard preprocessing and controlling for motion and physiological noise with regression. We computed the functional connectivity using four DMN seeds (medial prefrontal, posterior cingulate, and bilateral lateral parietal cortex) defined in a published independent dataset.
Results: Comparison of the average correlation map of the four DMN seeds between patients and controls revealed a cluster of stronger connectivity in patients in the medial prefrontal cortex (MNI: $x=14$, $y=66$, $z=28$; pFDR $< .005$). This region of significant group difference is part of the DMN, but not part of the seed.
Conclusions: Preliminary results show that patients with maladaptive self-focused attention demonstrate greater functional connectivity in the DMN when at rest, which may reflect greater internally-directed attention.
Supported By: NIMH K23109593
Keywords: Default Mode Network, Self-Conscious Emotions, Resting State, Resting State Functional Connectivity

S18. Interoceptive Prediction Signals in the Anterior Insula

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Background: Heightened anticipation of aversive experiences is a prominent feature of anxiety that involves the generation of interoceptive predictions about the state of the body. The current study investigated the neural circuits supporting this process during a pharmacological interoceptive perturbation.
Methods: 24 healthy individuals received randomized double-blinded bolus infusions of isoproterenol (0.5, 2 micrograms) and saline during BOLD fMRI scanning at 3 Tesla. Each dose was repeated twice. Throughout each infusion scan (4 minutes) participants attended to the overall intensity of perceived cardiac and respiratory sensations. To focus on anticipatory interoceptive signal processing under uncertain conditions, we examined areas exhibiting increased BOLD activity before and directly following saline infusion delivery.
Results: Activity in the bilateral ventral mid insula ($p<0.001$, corrected) increased immediately after saline delivery. However, during the period when physiological responses to isoproterenol typically peak, activation shifted to the anterior region bilaterally, while also maintaining mid insula activation in the right hemisphere ($p<0.001$, corrected). During the period when physiological responses to isoproterenol typically show early homeostatic recovery, activation expanded across the entire insula bilaterally ($p<0.001$, corrected) whereas during the late recovery period all insula activation subsided. Importantly, there were no significant changes in heart rate over the duration of the saline scans.
Conclusions: Dynamic shifts in insula activation can occur independent of physiological responses during periods of aversive interoceptive expectancy. These results provide evidence that the anterior insula is an integral component of interoceptive predictions.
Supported By: National Institute of Mental Health (NIMH) Award Number K23MH112949 (SSK), National Institute of

General Medical Sciences NIH/NIGMS P20GM121312 (SSK), and The William K. Warren Foundation
Keywords: Insula, Interoception, Anticipation, Anxiety, Homeostasis

S19. Memory Processes and Fear Conditioning: Preliminary Results

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Background: Fear acquisition and extinction are processes of implicit learning. Our aim was to evaluate, in healthy subjects and in OCD patients, if the performance on explicit memory tests could predict implicit learning in the fear conditioning paradigm.
Methods: Eight HS (4 women, mean age=36.5, SD=15.8) and 18 OCD patients (12 women, mean age=32.3, SD =7.5) were submitted to Logical Memory test and Rey-Osterrieth Complex figure (ROCF) before initiating a two-day fear conditioning paradigm. Explicit learning was evaluated through a questionnaire specifically designed for that purpose. Results were normalized as percent of maximum unconditioned skin conductance response (SCR) of each subject. The extinction retention index (ERI) was calculated as described in previous trials. Additional indexes were calculated as ratios between the expected higher and lower mean SCR. Spearman correlation was used to test associations between indexes and cognitive results.
Results: HS outperformed OCD patients in the ROCF immediate and late recall ($p=0.03$ and <0.01, respectively; Median Test). Patients and HS with complete or partial explicit learning of the paradigm did not differ significantly regarding memory tests performance (Median Test). Six HS and 15 patients passed SCR signal quality control. Four (66%) HS and 6 (40%) OCD patients presented ERIs below the overall median. No associations were found between indexes of fear learning, fear extinction, recall, renewal and the performance in memory tests (Spearman correlation).
Conclusions: We found no association between implicit and explicit memory performance regarding measures of implicit and explicit learning of the fear conditioning paradigm. This result warrants replication in larger samples.
Supported By: FAPESP, CNPQ
Keywords: Fear Conditioning and Extinction, Obsessive Compulsive Disorder (OCD), Verbal Memory, Visual Memory, Learning and Memory

S20. Error-Processing in OCD: A Meta-Analysis of fMRI Studies and Investigation of Changes Following CBT

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Background: Functional magnetic resonance imaging (fMRI) studies report brain activation abnormalities in obsessive-compulsive disorder (OCD) patients during error-processing and inhibitory control. However, conclusions are limited by small sample sizes. Moreover, few studies have examined whether brain response to errors and/or inhibitory control demands change with changes in OCD severity (e.g., pre- to post-treatment).
Methods: A Seed-based d Mapping (SDM) (www.sdmproject.com) fMRI meta-analysis using unthresholded t-maps compared patients with OCD and controls during error-processing and inhibitory control. Ten datasets including 239 patients with OCD (mean age range=14-39; mean CY-BOCS range=11-27) and 231 healthy controls (mean age range=14-40) were included. Preliminary data from an independent sample of 21 patients with OCD (8 adolescents and 13 adults, age=25.5, Y-BOCS=24.5) who completed a flanker task during fMRI before and after cognitive-behavioral therapy (CBT) was also examined.
Results: In the meta-analysis, patients with OCD, relative to controls, showed hyperactivation in right insula, bilateral inferior frontal gyrus (IFG), posterior medial frontal cortex (pMFC) and frontopolar cortex during error-processing, but hypoactivation in anterior cingulate cortex, right insula/IFG/putamen, orbitofrontal cortex and bilateral caudate during inhibitory control (SDM-$Z>2$, $p<.005$). Following CBT, patients showed decreased symptoms ($t(20)=8.47$,$p<.001$) and increased activation in right insula/putamen to errors ($p<.05$, SVC).
Conclusions: Findings are in line with reports in smaller cohorts, showing evidence for fronto-opercular hyperactivation during error-processing, but fronto-opercular and striatal hypoactivation during inhibitory control. Future work should examine whether hyperactivation during error-processing may compensate for hypoactive inhibitory control networks in OCD, given the upregulation of fronto-opercular response to errors that accompanied symptom reduction following CBT.
Supported By: RO1MH102242
Keywords: Obsessive Compulsive Disorder (OCD), Performance Monitoring, CBT, Error Monitoring, Meta-analysis

S21. Neural Mechanisms of Sensory Phenomena and Other Dimensional Symptoms in Obsessive-Compulsive Disorder

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Background: Sensory phenomena (SP) are aversive or uncomfortable sensations that drive repetitive behaviors in obsessive-compulsive and related disorders. SP contribute to symptom heterogeneity in OCD, and may be derived from a

distinct neural etiology. This study investigated functional neural activation in OCD patients with a range of SP severity to compare the relationship between brain activity and symptom severity among several core OCD symptoms including SP, harm avoidance (HA), perseverative thinking (PT), and perfectionism (Perf).
Methods: Severity of core symptoms was assessed in 17 OCD patients using a combination of clinical interview and self-report scales. FMRI data was acquired during performance of a task where subjects viewed short videos showing different body movements/sensations. Analyses of this preliminary sample utilized whole-brain regressions to examine the relationships between symptom severity and brain activity during task ($p<0.005$, uncorr).
Results: SP severity was not significantly related to any other symptoms (HA, PT, Perf), although HA and PT scores were significantly positively correlated ($r=0.61$, $p=0.007$). SP severity was positively related to activation in the insula, pre- and post-central gyri, amygdala, and hippocampus. When comparing the strength of correlations of brain activity with scale scores, SP was more strongly correlated with insula, pre- and post-central gyri, and mid-orbitofrontal cortex activity than the other symptoms.
Conclusions: SP are behaviorally and neurally dissociable from other core OCD symptoms and more strongly associated with activation of regions involved in interoception and sensorimotor processing. These findings may aid in the development of novel treatments to target specific symptoms in OCD.
Supported By: R01MH111794
Keywords: Obsessive Compulsive Disorder (OCD), Brain imaging, fMRI, OCD Symptom Dimensions

S22. Contributions of Minor Traumatic Brain Injury to the Development of Posttraumatic Stress Following Motor Vehicle Accident

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Background: The influence of minor traumatic brain injury (MTBI) on the pathogenesis of posttraumatic stress symptoms (PTSS) and posttraumatic somatic symptoms commonly termed “post-concussive” (PCS) remains poorly understood.
Methods: We evaluated the influence of MTBI on PTSS (IES-R) and PCS (adapted Rivermead Questionnaire) at six months among a large cohort of individuals presenting to the emergency department (ED) for care within 24 hours of motor vehicle collision (MVC). Sociodemographic, MVC details and presence of head strike were assessed.
Results: Among participants (948), 867 (91%) had six month follow-up data and were included in analyses. 369/867 (43%) reported head strike/injury during collision, of these 53/369 (14%) reported loss of consciousness (LOC) and 82/369 (22%) reported amnesia. In multivariable analyses adjusted for age, sex, and collision type, head strike did not predict PTS symptoms at six weeks ($RR = 1.16$, $p = 0.26$) or six months. Individuals who reported hitting their head during the collision had a higher number of PCS than individuals who did not report hitting their head (2.95 vs. 1.87, $t = 6.72$, $p < 0.001$). However, the majority of individuals who reported PCS did not hit their head. In addition, 68/369 (18%) of those who hit their head reported no PCS at six months.
Conclusions: Among a cohort of individuals presenting to the ED after MVC, minor head injury was not associated with increased PTSS at six months. Head strike was associated with increased PCS at six months, but was neither necessary nor sufficient for the development of PCS.
Supported By: NIAMS R01AR056328
Keywords: PTSD - Posttraumatic Stress Disorder, Head Impacts, Mild Traumatic Brain Injury

S23. Representations of Washing and Checking Symptoms in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a clinically heterogeneous disease washing and checking compulsions as the most prevalent clinical symptoms. Few neuroimaging studies investigated the neural correlates of the individual symptoms. It is not clear whether different symptoms are accompanied by different neural representations in the brain. In this study, we aim to investigate the representation of washing and checking using a combination of univariate and multi-variate pattern analysis (MVPA).
Methods: 24 OCD patients and 24 matched healthy controls were recruited in a functional magnetic resonance imaging (fMRI) experiment. Participants were scanned during a symptom provocation paradigm in which three conditions were involved: washing, checking and a neutral condition. The stimuli included pictures validated by OCD patients and therapists from Simon et al. and are designed to provoke compulsions.

Explorative MVPA was conducted in order to investigate whether different symptoms can be predicted from the activity patterns from brain regions including the amygdala, caudate, insula, anterior cingulate, OFC, striatum and thalamus.
Results: Our results demonstrated an enhanced recruitment of the right orbitofrontal cortex (OFC) in the OCD patients compared with the controls when viewing washing related images compared with the checking images. Moreover, the two different symptoms (washing vs checking) were successfully predicted above chance based on the neural patterns in the OFC.
Conclusions: Our results highlight the relevance of OFC in OCD and indicate that this region may be predominantly involved in the pathogenesis of washing compulsions. Moreover, OFC seems to have a separate representational format for different symptoms.
Supported By: DFG, German Research Foundation

Keywords: fMRI, Multivariate Classification, Obsessive Compulsive Disorder (OCD), Orbitofrontal Cortex, Neuroimaging

S24. The Influence of Acoustic Startle Probes on Fear Learning in Humans

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Background: Even though human fear-conditioning involves affective learning as well as expectancy learning, most studies assess only one of the two distinct processes. Commonly used read-outs of associative fear learning are fear-potentiated startle reflex (FPS), pupil dilation and self-reported anxiety. A clear asset of FPS is that it reflects the affective aspect of fear learning, while pupil dilation reflects a general arousal response. However, in order to measure FPS, aversively loud acoustic probes are presented during conditioning, which might in itself exert an effect on fear learning.
Methods: We tested the effect of startle probes on fear learning by comparing brain activation (fMRI), pupil dilation and self-reported anxiety with and without acoustic startle probes within subjects (n=26). fMRI: voxel-wise statistical tests were family-wise error rate corrected for multiple comparisons ($p<0.05$) for the whole brain or regions of interest, using threshold free cluster enhancement with 5000 permutations. We used Bonferroni correction for six ROIs.
Results: Regardless of startle probes, fear conditioning resulted in enhanced dorsal anterior cingulate cortex($p<.001$), insula($p=.019$) and ventral striatum($p<.001$) activation. Interaction analyses showed that startle probes diminished differential pupil dilation ($p<.05$) between the reinforced conditioned stimulus (CS+) and the unreinforced conditioned stimulus (CS-) due to increased pupil responses to CS-. A trend significant interaction effect was observed for self-reported anxiety($p=.06$) and amygdala activation($p=.029$).
Conclusions: The increased pupil response to the CS- suggests that startle probes might affect fear learning in a counterintuitive way: instead of enhancing fear learning it reduced discriminative fear learning by increasing arousal to the CS-.
Supported By: Vici grant from the Netherlands Organization for Scientific Research and an Amsterdam Brain and Cognition project grant from the University of Amsterdam
Keywords: Fear Conditioning, Fear-Potentiated Startle Reflex, Pupil Dilation, fMRI, US-Expectancy

S25. Brain Activation of Fear Associated Learning During Early Post-Trauma Period

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Background: It has been proposed that deficits in fear-associated learning contribute to the development of post-traumatic stress disorder (PTSD) and chronic pain after a traumatic injury. A fear associated learning task (FALT) has revealed altered brain activations associated with fear and safety learning in patients with chronic PTSD and pain; however, FALT brain activations have never been studied in the early post-trauma period. Thus, possible links between FALT brain activation and symptoms of early post-trauma are still unknown. This study examined FCT brain activation within weeks after traumatic injury to investigate this issue.
Methods: Within 2 weeks after a traumatic injury, 50 trauma survivors underwent a FALT, comprised of acquisition, extinction, and extinction recall phases during fMRI brain scans. Symptoms were assessed with the PTSD Check List (PCL), Acute Stress Disorder Questionnaire (ASDQ), Pain Anxiety Symptom Scale (PASS), and Pain Catastrophizing Scale (PCS).
Results: A contrast between conditioned stimuli that were (CS+) or were not (CS-) paired with an aversive stimulus revealed activations in the medial-prefrontal/dorsal anterior cingulate (mPFC/dACC), right insula (IC), and right dorsolateral prefrontal (dlPFC) cortices during acquisition; sensorimotor, right dlPFC and superior lateral-occipital/superior parietal (slOC/SPC) cortices during extinction; left IC and right slOC cortices during recall. Negative correlations were significant between mPFC/dACC activation during acquisition and both PASS and PCS scores.
Conclusions: The results suggest emotion regulatory activation in mPFC during fear learning is associated with pain stress symptoms within weeks following trauma. Further studies will examine the relationships between early FALT activations and chronic symptoms.
Supported By: R0IMH110483
Keywords: Fear Conditioning and Extinction, Pain, PTSD - Posttraumatic Stress Disorder

S26. Smaller Hippocampal Volume Predicts the Development of Posttraumatic Stress Disorder Following Sexual Assault in Females

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Background: Exposure to sexual assault is a significant risk factor to develop posttraumatic stress disorder (PTSD), particularly in females. The early neurobiological changes leading to the development of PTSD remain however, understudied and unclear in this population.
Methods: Participants were 25 female victims of sexual assault recruited 1 month following exposure to sexual assault (T1) and 20 age-matched non-exposed healthy controls. Among the victims, 10 participants met (PTSD+) and 15 did not meet (PTSD-) DSM-IV criteria for PTSD 6 months post-trauma (T2). At both visits, participants underwent structural magnetic resonance imaging and salivary cortisol samples were collected through the day (8am, 12pm, 4pm, 8pm). Hippocampal volumes were extracted and individually adjusted for total intracranial volume. Individual areas under the curve relative to the ground (AUCg) were calculated as indices of

total diurnal cortisol changes. Non-parametric statistics were used to compare measures at T1 between groups at T1, measures at T2 between groups at T2, and measures at T1 between groups at T2.
Results: At T1, victims had significantly smaller hippocampal volumes than controls (left: p=0.004, r=-0.43; right: p=0.022, r=-0.34), but AUCg did not significantly differ between groups. At T2, neither hippocampal nor AUCg significantly differed among the groups. However, hippocampal volumes at T1 were significantly smaller in the PTSD+ group relative to the control group (left: p=0.021, r=-0.50; right: p=0.029, r=-0.48), but not the PTSD- group.
Conclusions: This study indicates that having smaller hippocampal volumes is a risk factor to develop PTSD for females exposed to sexual assault.
Supported By: Hospital Clinical Research Program; Fondation Pierre Deniker; SFR FED4226 Neuroimagerie Fonctionnelle; French Ministry of Higher Education, Research and Innovation
Keywords: PTSD - Posttraumatic Stress Disorder, Sexual Assault, Hippocampal Volume, Cortisol

S27. Predicting Trauma-Focused Therapy Outcome From Resting-State Functional Magnetic Resonance Imaging in Veterans With Posttraumatic Stress Disorder

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Background: Trauma-focused psychotherapy is the first-line treatment for posttraumatic stress disorder (PTSD) but 30-50% of patients do not benefit sufficiently. Here, we tested whether resting-state functional magnetic imaging (rs-fMRI) can predict treatment response for individual patients.
Methods: 44 male veterans with PTSD underwent baseline rs-fMRI scanning followed by trauma-focused therapy (EMDR or TF-CBT). Resting-state networks (RSN) were obtained using independent component analysis with 70 components on the basis of 28 trauma-exposed healthy controls, matched for age and gender. Dual regression was used to obtain subject-specific RSNs for the PTSD patients. All RSNs were individually included in a machine learning classification analysis using Gaussian process classifiers. Classifier performance was assessed using 10 times repeated 10-fold cross-validation.
Results: Patients were grouped into treatment responders (n = 24) and non-responders (n = 20), based on a 30% decrease in total clinician-administered PTSD scale for the DSM-IV (CAPS) score from pre- to post-treatment assessment. A network centered around the pre-supplementary motor area achieved an average accuracy of 81% ($p < 0.001$, based on a permutation test, corrected for multiple comparisons across 44 signal components), with a sensitivity of 84.5%, specificity of 77.5%, and area under receiver-operator curve (AUC) of 0.93.
Conclusions: Rs-fMRI recordings are capable of providing personalized predictions of treatment response in a sample of veterans with PTSD. It therefore has the potential to be useful as a biomarker of treatment response and should be validated in larger independent studies.
Supported By: ZonMw; AMC; Dutch Ministry of Defense
Keywords: PTSD Treatment, Multivariate Classification, Machine Learning, Resting-State fMRI, Resting State Networks

S28. Neurobiologically Derived Clusters Differentiate Youth Based on Internalizing Symptom Load

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Background: The structure and function of the default mode network (DMN) has been associated with internalizing disorders. Behavioural and neurobiological heterogeneity as well as the presence of nonlinear brain behaviour relationships likely contribute to inconsistent results in this literature.
Methods: Here we examine internalizing symptoms in relation to patterns of 1) DMN resting state functional connectivity, and 2) DMN region volumes, in a large community sample of children and youth (Philadelphia Neurodevelopmental Cohort; N=713). A data-driven clustering approach based on participant similarity network fusion is used to identify groups of individuals with similar DMN structure and function.
Results: Grouping similar participants based on DMN structure and function revealed three clusters that differed in mean number of internalizing symptoms. Functional connectivity was highest in group with the highest symptom load, intermediate in the group with the lowest symptom load and lowest in the group with an intermediate symptom load. This pattern was particularly pronounced for functional connection between anterior and posterior DMN regions. DMN region volumes were largest in group with lowest symptom load. Linear relationships between number of symptoms and DMN structure and function were not significant.
Conclusions: By combining information about DMN structure and function from different imaging modalities we identify groups of individuals with similar DMN patterns that are associated with differing levels of symptoms of depression and anxiety. These relationships were not apparent when examining linear brain behaviour relationships or when clustering participants based on functional or structural DMN information alone. These groups may reflect distinct etiopathology related to internalizing symptoms.
Supported By: SickKids Foundation
Keywords: DMN, Internalizing Symptoms, Similarity Network Fusion

S29. Targeting the Reconsolidation of Traumatic Memories With Electroconvulsive Therapy and Prolonged Exposure Therapy in Posttraumatic Stress Disorder

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Background: Traumatic memories are particularly persistent, which probably underlies the significant rates of treatment failure observed in Posttraumatic Stress Disorder (PTSD). We explored whether interventions for PTSD that also interfere with the reconsolidation of aversive memories, namely, Prolonged Exposure (PE) and Electroconvulsive Therapy (ECT), could have their effects augmented if delivered during the reconsolidation of the traumatic memories.
Methods: In study 1, subjects with PTSD where randomly assigned to receive two sessions PE therapy either after retrieving their traumatic memories (n=21) or a neutral memory (n=21). In study 2, severe, treatment-resistant PTSD received 6 sessions of ECT either after retrieving their traumatic (n=4) or a neutral memory (n=4). Skin Conductance Responses (SCR) and subjective reactivity (state scales for mood, anxiety and PTSD) to a recollection of their traumas were obtained both before and after the interventions in both studies.
Results: Reductions in reactivity to the traumatic imagery were pronounced if PE was preceded by traumatic retrieval in the case of SCR ($p = 0.039$), but not for subjective reactivity ($p > 0.33$) except for responses measured by one of the PTSD scales (IES-R), which was favorable to the neutral retrieval group ($p = 0.034$). Post traumatic-retrieval ECT tended to produce more pronounced reductions SCR and subjective reactivity to the traumatic imagery, reaching statistical significance when measured by the STAI state ($p = 0.026$) and a trend significance VASs and the state versions of the DTS and POMS.
Conclusions: Reconsolidation-based treatments are promising targets of investigation in PTSD, even for more complex cases.
Supported By: State of São Paulo Research Foundation (FAPESP) – grant #2014/04810-0 to Felipe Corchs.
Keywords: PTSD - Posttraumatic Stress Disorder, Reconsolidation, Fear Memory, Modified Electroconvulsive Therapy (ECT), Exposure Therapy

S30. Posttraumatic Stress Disorder Onset and Inflammation-Related Biomarkers in Civilian Women

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Background: Research has linked PTSD with higher circulating levels of inflammation-related biomarkers, and effects may be bidirectional. Not only may PTSD lead to elevated inflammation, but inflammation may contribute to increased susceptibility to PTSD. We conducted the first investigation of new-onset PTSD and changes in inflammation-related biomarkers.
Methods: Data were from women in the Nurses' Health Study II. Biomarkers obtained at two blood draws, 10-16 years apart, included C-reactive protein (CRP), tumor necrosis factor-alpha receptor-II (TNFRII), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). PTSD was assessed via interview. Analyses compared biomarker levels in women with PTSD that onset between draws (n=175) to women with no history of trauma (n=175) and to women with history of trauma at draw 1 and no PTSD at either draw (n=175). We examined if PTSD onset was associated with biomarker change over time and if pre-PTSD-onset biomarker levels indicated risk of subsequent PTSD using linear mixed models and linear regression, respectively. Biomarkers were log-transformed.
Results: Compared to women without trauma, women in the PTSD onset group had larger increases in VCAM-1 over time (b=0.003, p=.068). They also had higher TNFRII (b=0.05, p=.049) and ICAM-1 (b=0.04, p=.060) at draw 1 (before trauma/PTSD onset). However, pre-PTSD-onset biomarkers did not predict onset of more severe PTSD (bs: -0.26 to -3.58, ps: .272 to .918).
Conclusions: PTSD onset was associated with increases in one inflammation-related biomarker. Effects may be small and cumulative; longer follow-up with larger samples is needed. We did not observe strong support that pre-PTSD-onset biomarkers predicted subsequent PTSD risk.
Supported By: This study was supported by the National Institutes of Health grants R01MH078928, R01MH101269, UM1CA176726, K01HL130650, and T32MH017119, as well as the Yerby Postdoctoral Fellowship Program.
Keywords: Inflammation, PTSD, Endothelial Function, Biomarkers, Women

S31. Most Sexual Assault Survivors With Significant Posttraumatic Stress do not Receive Mental Health Care in the Initial Weeks After Assault

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Background: Little data exists regarding receipt of mental health care services by sexual assault (SA) survivors in the early aftermath of SA.
Methods: Women SA survivors ≥18 years of age who presented for emergency care within 72 hours of assault to one of the 12 sexual assault centers in the Better Tomorrow Network were enrolled. Six-week follow-up assessment included an evaluation of posttraumatic stress symptoms (PTSS, DSM-IV PCL, score ≥ 30 defined significant PTSS) and health care services received. Qualitative comments were collected regarding barriers to care.
Results: To date 411 women have been enrolled and 337/411(82%) have completed six-week follow-up assessment. 294/337 (91%) had significant PTSS at six weeks. The most common types of health care providers seen by women with significant PTSS were primary care providers (111/294 (38%)), mental health providers (93/294 (32%)), and OB/GYN providers (33/294 (11%)). The most common types of mental health care providers seen were psychiatrists (49/93 (53%)), psychologists (46/93 (49%)), and social workers (15/93 (16%)). Women with significant PTSS who saw a provider did not always disclose their SA: 26 (23%) did not tell their PCP, 4 (12%) did not tell their OB/GYN, and 3 (3%) did not tell their mental health provider. Qualitative comments regarding barriers to care will be summarized.
Conclusions: Nearly 7 in 10 women SA survivors with significant post-assault PTSS do not receive mental care services during the initial six weeks after assault. Efforts to develop and test early interventions in this population are needed.
Supported By: R01AR064700
Keywords: Sexual Assault, Women's Health, PTSD - Posttraumatic Stress Disorder

S32. Psychological Resilience Following Sexual Assault Predicts Improved Mental Health Outcomes

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Background: Sexual assault (SA) occurs to one in five US women and is associated with a range of adverse neuropsychiatric outcomes, including posttraumatic stress and depressive symptoms. Characteristics associated with increased psychological resilience in the early aftermath of SA remain poorly understood.
Methods: Biosex female women presenting for emergency care after SA were enrolled. Assessments one week after SA included evaluation of sociodemographic characteristics, psychological resilience (PR, 5 items from CIDI), and reported pre-SA health, including posttraumatic stress (PTS, abbPCL), depressive symptoms (PROMIS), anxiety symptoms (PROMIS), lifetime trauma (LEC), pain intensity (0-10 scale), and global mental and physical health (PROMIS). Assessments six weeks after SA included PTS (PCL-S), depressive symptoms, anxiety symptoms, and global mental and physical health.
Results: Among participants enrolled to date (n=422), 338/422 (80%) have completed six-week follow-up. Increased educational attainment was associated with increased PR, but not income. Increased PR one week after SA was associated with better pre-SA health: reduced PTS [r=-.155(.003)], depressive symptoms [r=-.365(<.001)], anxiety symptoms [r=-.340(<.001)], prior trauma [r=-.136(.007)], past pain [r=-.130(.010)], and improved global mental [r=.456(<.001)] and physical [r=.290(<.001)] health. Increased PR one week after SA predicted reduced depressive symptoms at six weeks [r=-.141(.011)] and increased global mental health [r=.140(.005)], but not reduced PTS or anxiety symptoms.
Conclusions: Increased PR one week after SA predicts reduced depressive symptoms and improved global mental health at six weeks. Reduced lifetime trauma and better pre-SA mental and physical health are associated with increased peritraumatic PR. Further studies are needed to better understand and augment resilience after SA.
Supported By: R01AR064700
Keywords: Resilience, Sexual Assault, Women's Mental Health

S33. The Effects of Early Life Stress on Fear Generalisation

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Background: Early life stress increases the risk of developing anxiety, and in this study we examined whether this might be due to the impact of early life stress on fear generalisation. Other research suggests that anxiety leads to greater generalisation, yet the relationship between early life stress has not been examined.
Methods: Rats were exposed to maternal separation (i.e., MS), a model for early life stress, where pups were separated from the dam on postnatal days 2-14, or reared as normal (i.e., standard reared, SR). In adulthood, rats received context conditioning and were tested for fear to the conditioning context or to a similar, but novel, context.
Results: SR rats showed higher levels of fear to the conditioning context compared to the similar context (p=.01), whereas MS rats displayed high fear to both contexts (p>.05) when tested the day after training. MS rats did discriminate

when tested after one hour (p=.004). All rats showed generalisation seven days after training (ps>.05). Neither a reminder prior to testing nor pre-exposure to the conditioning context before training attenuated generalisation in MS rats (ps>.05).
Conclusions: In summary, early life stress results in a more rapid rate of generalisation. This increased generalisation does not stem from a failure to discriminate, with MS rats showing discrimination when tested one hour after training. Manipulations previously shown to attenuate generalisation in SR animals did not reduce generalisation in MS animals. Thus, early life stress may increase vulnerability to later-life anxiety by enhancing fear generalisation.
Supported By: ARC
Keywords: Early Life Stress, Fear Generalization, Context Generalization

S34. New Onset Anxiety and Anxiety Exacerbation in the Perinatal Period: A Systematic Review and Meta-Analysis

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Background: Nearly 1 in 5 women will have an anxiety disorder during the perinatal period, yet the risk factors for these problems are not well understood. The present systematic review and meta-analysis aimed to identify risk factors of both new onset anxiety and anxiety worsening during pregnancy and the first year postpartum.
Methods: Published articles in PubMed, MEDLINE, PsycINFO, CINAHL, Ovid Portal, ProQuest Portal, and Web of Science Portal were searched from their inceptions to September 2017. Studies assessing risk factors for the development of new onset anxiety (defined as anxiety occurring in women without a pre-existing anxiety disorder), and anxiety worsening (worsening of symptoms in women with pre-existing anxiety disorders), were eligible.
Results: A total of 11,759 studies were identified, with 11 meeting our eligibility criteria. Prenatal oxytocin exposure (OR=1.44, 95% CI=1.31-1.58), poorer educational attainment (OR=1.88, 95% CI=1.17-3.03), comorbid sleep disorders (OR=1.98, 95% CI=1.10-3.59), and a family history of OCD (OR=20.45, 95% CI=5.90-70.91) were significant predictors of new onset anxiety, while prenatal oxytocin exposure (OR=1.50, 95% CI=1.26-1.79) and comorbid psychiatric disorders (OR=2.83, 95% CI=1.39-5.76) were risk factors for worsening.
Conclusions: While a range of factors predicted new onset anxiety and anxiety worsening, prenatal oxytocin exposure was a significant factor of both. This particular finding may contribute to the current body of knowledge on the pathophysiology of anxiety disorders occurring in the perinatal period. Additional research is required in order to further investigate these risk factors and to determine whether they differ from non-puerperal populations.
Keywords: Anxiety Disorders, Pregnancy, Postpartum, Risk Factors

S35. Evidence for PACAP as a Biomarker for Anxiety Disorders in Women

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Background: Pituitary adenylate cyclase activating polypeptide (PACAP) is a neurohormone released in the hypothalamus and adrenal gland thought to modulate the HPA axis. In females with PTSD, circulating PACAP levels have been correlated with symptoms. Given that patients with anxiety-spectrum disorders have maladaptive responses to stress, we hypothesize that circulating PACAP will correlate with generalized anxiety disorder diagnoses.
Methods: Serum samples from 211 adults with generalized anxiety disorder (GAD, n=91), posttraumatic stress disorder (PTSD, n=8), and healthy controls (HC, n=112), formally assessed at MGH Center for Anxiety and Traumatic Stress Disorders, were assayed for PACAP by radioimmunoassay. Data were analyzed by 3-way ANCOVA, testing diagnosis, gender, and use of psychotropic medications, with sample collection time as a covariate. The GAD samples were genotyped for PAC1R SNP associated with elevated symptoms of PTSD.
Results: There was no effect of blood draw time on PACAP level. The overall outcome of the analysis of interaction of diagnosis, gender, and psychotropic medication use was non-significant (p=0.2). When serum PACAP was stratified by genotype data for the rs2267735 SNP, there is a non-significant positive association of the known high-risk CC genotype with elevated PACAP levels and with elevated anxiety symptoms, particularly somatic symptoms, in females with GAD.
Conclusions: These initial data suggest sex differences in circulating levels of PACAP, but PAC1R SNP is a better biomarker for anxiety, as with PTSD. Notably, mode of assay and sample handling is particularly important for the study of PACAP and greater sample sizes may also be needed.
Supported By: Highland Family Foundation
Keywords: Biomarkers, Anxiety, Sex Differences, Translational Research, SNP

S36. Reappraisal of Personal Criticism in Social Anxiety Disorder: A Brain Network Perspective

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Background: Social anxiety disorder (SAD) is characterized by difficulties with emotion reactivity and cognitive reappraisal

in a social context; together form emotion dysregulation. Adaptive emotion regulation is thought to involve functional connectivity between emotion reactivity and cognitive reappraisal brain networks. Yet, it remains unclear what is the effective connectivity within and between these networks under emotional context.
Methods: During our fMRI task, 70 SAD patients and 25 healthy controls (HC) were instructed to react naturally or reappraise their emotional reactivity to video clips of actors delivering social criticism. We used a graph-theory method called Dependency Network Analysis (DEPNA) which captures the network hierarchy by quantifying each region's effective connectivity (termed influence) in the network. DEPNA was implemented to investigate intra- and inter-network influences in a priori defined emotion reactivity and reappraisal brain networks under socially negative emotional context.
Results: During the react condition there were no significant differences between the groups. However, during reappraisal, the right inferior frontal gyrus (rIFG) showed significantly reduced influence both on cognitive reappraisal and emotional reactivity networks among SAD patients compared to HC. Importantly, a higher influence of the rIFG during reappraisal associated with greater reappraisal success in SAD. Surprisingly, SAD patients' bilateral amygdala exhibited reduced influence on the reappraisal network compared to HC.
Conclusions: These findings emphasize that bi-directional influences of nodes in both networks on each other may underlie efficient emotion regulation of social context via cognitive reappraisal. We propose that the influencing degree of regions may serve as a target for connectivity-based diagnosis and neuromodulation therapies.
Supported By: This work was supported by the Israeli Centers of Research Excellence and the Israeli Ministry of Science, Technology and Space, as well as the National Institute of Mental Health.
Keywords: Emotional Dysregulation, Brain Imaging, fMRI, Graph Theory, Social Anxiety Disorder, Cognitive Reappraisal

S37. Neural Evidence for Altered Learning Mechanisms in Posttraumatic Stress Disorder

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Background: Exposure to interpersonal violence is a risk factor for several psychopathologies, including posttraumatic stress disorder (PTSD). Though therapeutic treatments have inconsistent success, the most effective treatments for PTSD involve exposure therapy, which relies on a fear-extinction learning model. A wide body of research indicates that individuals with PTSD show a heightened sensitivity to fearful stimuli and decreased fear extinction learning, though it is likely that these learning deficits may also generalize to neutral, non-fearful contexts. This study utilizes a neutral reinforcement-learning task and behavioral modeling to examine the neural correlates of learning deficits in PTSD with the goal of improving evidence-based treatment strategies for the disorder.
Methods: 29 adult females (15 PTSD with exposure to assaultive violence, 14 controls) underwent a neutral reinforcement-learning task in fMRI in which they were instructed to invest money in one of two doors, receiving money back if that door was unlocked. We used modified versions of the Rescorla-Wagner learning model to computationally model participant behavior and Independent Component Analysis to track neural network response to the task between groups.
Results: Eighteen component networks were identified. Women in the PTSD group demonstrated a significant decrease in neural encoding of prediction error in both the reward-valuation ($p=0.0172$) and insula networks ($p = 0.0061$) as compared to healthy controls.
Conclusions: We report data that support the hypothesis of a deficit in neural encoding of prediction errors in PTSD outside of a fearful or social context, evidenced by reduced neural network activity in the PTSD group on a neutral reinforcement-learning task.
Supported By: NARSAD
Keywords: PTSD - Posttraumatic Stress Disorder, Computational Modeling, Independent Component Analysis, Reinforcement Learning

S38. Epigenetic Modification of the Oxytocin Receptor Gene Impacts Infant Neural Response to Emotional Faces

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[1]University of Virginia

Background: The human brain's capacity to detect and discriminate between emotional facial expressions emerges early in ontogeny. However, little is known about specific biological factors that contribute to variability in this vital social skill during infancy. In adults, DNA methylation of the oxytocin receptor gene (OXTR) is an epigenetic modification that is variable, predictive of gene expression, and has been linked to autism spectrum disorder (ASD) and the neural response to social cues. It is unknown whether OXTR methylation is variable in infants, and whether it may be predictive of social function.
Methods: Implementing a developmental neuroimaging epigenetics approach, we examined whether OXTR methylation impacts brain responses to emotional faces. We presented a large sample of seven-month-old infants (N=84) with happy, angry, and fearful faces while recording functional near-infrared spectroscopy (fNIRS). OXTR methylation was measured from saliva through a procedure validated with adults.
Results: An interaction of OXTR methylation and facial emotion was revealed in the right inferior frontal cortex ($F(2, 160) = 6.223$, $p = 0.002$), a region implicated in emotion understanding that exhibits atypical function in ASD. Specifically, higher levels of OXTR methylation, and a presumably reduced ability to use endogenous oxytocin, were associated with enhanced responses to anger and fear and attenuated responses to happiness.

Conclusions: Findings support accounts emphasizing oxytocin's role in enhancing approach while reducing withdrawal tendencies during social interactions. Moreover, we identify OXTR methylation as an early-emerging biomarker contributing to variability in social brain function at its earliest stage.
Supported By: Max Planck Society, University of Virginia, NSF
Keywords: Infancy, Oxytocin, fNIRS, Epigenetics, Emotion Perception

S39. The Association Between Mother-Infant Attachment Disorganization and Cortisol Attunement

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Background: Dysregulated cortisol secretion and disorganized mother-infant attachment are well-established risk factors for later psychopathology (Jessop & Turner-Cobb 2009; Lyons-Ruth & Jacobvitz, 2016). Mother-infant cortisol attunement is important to study because infants rely on their mothers for regulation, and attunement represents a physiological reflection of the dyad's shared emotional and behavioral experiences (Atkinson et al., 2016). Despite theoretical links, however, cortisol attunement has never been studied in relation to mother-infant attachment disorganization.
Methods: With a large community sample ($n = 314$), this study investigated associations between mother-infant attachment disorganization and cortisol attunement. Disorganization and cortisol attunement were assessed during the Strange Situation Procedure (SSP) at infant age 17 months. Salivary cortisol was collected at baseline, and 20 and 40 minutes post-SSP. Data was analyzed using three approaches to probe different definitions of attunement: correlated growth modelling, cross-lagged modelling, and difference score analyses.
Results: The correlated growth model revealed that cortisol trajectories in disorganized dyads, relative to organized dyads, were significantly correlated, such that, among disorganized dyads, as infants had greater increases in cortisol, mothers had greater decreases in cortisol ($b = -.03$ $SE = .01$, $p < .05$). The cross lagged model revealed no associations between disorganized attachment and attunement when defined as both reciprocal and lagged. Difference score analyses revealed that disorganized (relative to organized) dyads had greater divergence between maternal and infant cortisol values ($b = -.07$, $p < .05$).
Conclusions: Findings suggest that disorganized attachment is a marker of maternal difficulty physiologically regulating her infant.
Supported By: CIHR, CAMH, and Ryerson University
Keywords: Cortisol, Attunement, Infant Attachment, Mother, Strange Situation Procedure

S40. Estradiol Modulation of Female Adolescent Emotion Regulation

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Background: There is accumulating evidence that brain activity during emotion and cognitive tasks is altered by hormone changes across the menstrual cycle. Specifically, high estradiol appears to be relevant to successful emotion generation and regulation as it enhances prefrontal cortex-mediated function. Thus, estradiol might alter the way girls' brains engage when using a reappraisal-based emotion regulation strategy to alter their emotional reactions. This study examined for the first time the association between estradiol levels and brain activation during an emotion regulation fMRI task in girls. Our purpose was to determine whether estradiol modulation during emotion regulation primarily occurred in cortical regions, subcortical regions or both.
Methods: Twenty-seven healthy adolescent girls underwent fMRI using Human Connectome Project-compatible methods and provided saliva samples to assay estradiol upon waking on fMRI-scheduled days. During fMRI, participants were instructed either to view neutral control images or to "Increase" or "Decrease" their initial emotional reactions to positive and negative images using reappraisal. Reported findings survived False Discovery Rate whole brain correction.
Results: During "View Negative" trials, greater estradiol was associated with greater activation in dorsolateral prefrontal cortex consistent with enhanced prefrontal function when processing negative images. When participants increased reactions to positive images, greater estradiol predicted lower activation in left dorsolateral prefrontal regions ($p = .04$).
Conclusions: This study shows that estradiol modulates emotion regulation-related brain activity in cortical regions. However, enhancement or suppression of brain activation depended on the valence of the emotion being regulated. Results suggest refinement of "top-down" prefrontal regulation theories is needed to explain different neuroendocrine effects.
Supported By: R01MH102854
Keywords: Estradiol, Emotion Regulation, Reappraisal, Adolescence

S41. Adverse Childhood Experiences are Associated With Altered Human Adult Gut Microbiome

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Background: Early life stress (ELS) produces an altered adult gut microbiome in rodents. The impact of ELS on adult microbiome in humans is unknown but may have implications for microbiome-gut-brain axis function. We assessed relationships between ELS and gut microbiome composition in psychiatrically healthy pregnant women.

Methods: Women were recruited from a study examining ELS and pregnancy outcomes. Participants completed the Adverse Childhood Experiences (ACE) questionnaire to indicate ELS exposure. Stool was sampled at 20-26 weeks gestation; 16S sequencing was performed and products analyzed using Illumina MiSeq. Alpha diversity was measured in operational taxonomic units (OTUs) at 10,000 read depth and Shannon index. Beta diversity was measured with un/weighted UniFrac distances. Differential abundance was assessed in taxa with >1% mean abundance across samples; multiple tests were corrected with the Benjamini-Hochberg method; false discovery rate (fdr) < 0.05 were considered significant. Permutation Multivariate Analysis of Variance (PERMANOVA) tested associations of microbiome composition with ACE.
Results: n = 48 women provided gut microbiome and ACE data. High (>=2) and low (<2) ACE participants were similar in demographics and psychiatric health. High ACE participants had higher relative abundance of Bacteroides (fdr=0.004), Ruminococcaceae (fdr=0.03), Faecalibacterium (fdr=0.007), Dialister (fdr=0.02), Enterobacteriaceae (fdr=0.01), and lower relative abundance of Eubacterium (fdr=0.004), and Phascolarctobacterium (fdr=0.002) versus low ACE. There were no differences between ACE groups for richness (p=0.82), Shannon index (p=0.58), nor UniFrac distances (p's>0.05).
Conclusions: A novel finding in humans, exposure to multiple ACEs was associated with differential abundance of several gut taxa in psychiatrically healthy adults.
Supported By: March of Dimes, NIMH K23, NARSAD Young Investigator Award
Keywords: Early Life Stress, Gut Microbiome, Adverse Childhood Experiences, Pregnancy, Prenatal

S42. Maternal Immune Activation Downregulates Microglia Proliferation in the Developing Brain

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Background: Neurodevelopmental diseases are often associated with viral infection during pregnancy. In mice, Maternal Immune Activation (MIA) results in cognitive and social abnormalities of the offspring at adulthood. We hypothesized that MIA might impact the developing microglia, via interferon type-I signaling, which thereby perturbs the normal brain development.
Methods: Pregnant dams were injected with the viral mimetic poly(I:C), or PBS as a control, 14.5 days following gestation (E14.5). Microglia isolated from their offspring were compared using high-throughput mRNA sequencing (RNA-seq) and flow cytometry analysis for the proliferation marker Ki67. Embryonic yolk sac, the origin of microglia in the developing offspring, was examined by RTqPCR on E15.5. To manipulate maternal interferon type-I signaling we treated pregnant dams either with anti-interferon type-I receptor (aIFNAR) antibodies, one day prior to the MIA, or with IFNb instead of poly(I:C).
Results: Newborn microglia showed reduction in expression of genes related to proliferation and cell cycle. This was confirmed by Ki67 flow cytometry analysis (n=8, t(14)=5.789, p< 0.0001). Yolk sac RTqPCR showed a signature of genes related to type-I interferon, following MIA. Maternal aIFNAR treatment prevented some of the effect of MIA on the newborn microglia (n=12, t(22)=1.735, p=0.0484). MIA by IFNb led to a reduction in Ki67 expression relative to control samples, which recapitulate to some extent the effect of poly(I:C) (n=6-7, t(11)=3.266, p= 0.0075).
Conclusions: Our results suggest that immune activation during pregnancy upregulates maternal interferon type-I that in turn interferes with the microglia programmed development cascade, which could impact neurodevelopmental phenotype at adulthood.
Keywords: Microglia, Maternal Immune Activation, Proliferation, Interferon-Beta

S43. Early Maternal Deprivation Induces Microglial Activation, Alters Glial Fibrillary Acidic Protein Immunoreactivity and Indoleamine 2,3-Dioxygenase During Development of Offspring Rats

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Background: Maternal deprivation (MD) induces behavioural changes and impacts brain circuits that could be associated with the pathophysiology of depression.
Methods: This study investigated markers of microglia and astrocytes activation, and indoleamine 2 3-dioxygenase (IDO) expression in developmental programming after early life MD (postnatal days (PND) 20, 30, 40, and 60).
Results: On PND 60, rats subjected to MD displayed a depressive-like behaviour. On PND 10 and 20, glial fibrillary acidic protein (GFAP) immunopositive cells were decreased in the hippocampus and prefrontal cortex (PFC) of rats subjected to MD. An increase in the GFAP immunopositive cells in the hippocampus was observed on PND 40 and 60 in MD rats. Iba-1 (microglia marked) were increased on PND 10, 20, and 30. IDO expression was reduced in the hippocampus on PND 10, and elevated within the PFC on PND 60 following MD. AIF-1 (microglia marked) expression increased in the PFC on PND 20 and 60 following MD.
Conclusions: Early life stress induces negative developmental programming in rats, marked by depressive-like behaviour in adult life. Moreover, MD increases microglial activation in early and late developmental phases. Levels of GFAP and IDO decreased in the early stages, but were higher in later developmental periods. These findings suggest that MD could differentially affect the expression of the IDO enzyme, beyond astrocyte and microglial cells. The onset of an inflammatory state from resident brain cells could be associated with the activation of the kynurenine pathway and the development of depressive behaviour in adulthood.

Supported By: CNPq (Brazil); FAPESC (Brazil); UNESC (Brazil).
Keywords: Microglial Activation, Maternal Deprivation, Depression

S44. Catch-Up Growth, Metabolic and Inflammatory Outcomes Among Post-Institutionalized Romanian Adolescents

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Background: Children reared in institutions often experience growth restriction and catch-up growth after adoption (Van Ijzendoorn et al., 2008). A shift from impaired perinatal growth to rapid postnatal weight gain confers risk for metabolic disease and inflammation (Barker et al., 2002), but no work has examined the metabolic and inflammatory outcomes linked to patterns of catch-up growth in post-institutionalized adolescents.
Methods: We prospectively followed institutionalized infants randomized to care as usual (n=68) and foster care intervention (n= 66), and community controls (n=127) (N=261) from Bucharest, Romania, across 16 years. Using latent class growth analysis, we derived trajectories of body mass index (BMI) at baseline (M age= 20.44 months), 30 months, 42 months, and ages 8, 12, 16. At age 16, participants provided dried blood spots, from which metabolic markers and pro-inflammatory cytokines were derived.
Results: Four BMI trajectories emerged, including average-stable (46.6%), low-stable (17.9%), elevated (20.7%), and accelerated (14.8 %). The accelerated trajectory, reflective of rapid catch-up growth, was comprised predominately of children randomized to foster care, who exhibited higher levels of glycosylated hemoglobin (HbA1c) and C-reactive protein compared to the adolescents in the other three trajectories. Additionally, a greater proportion of the foster care group was overweight/obese compared to the care as usual group (OR= 4.50, CI= 1.46 to 13.89).
Conclusions: While catch-up growth is viewed as a positive improvement among post-institutionalized children, continuous and rapid increases in body size poses a health concern. These results have implications for monitoring weight gain, diet, and physical activity of adopted children.
Supported By: John D. and Catherine T. MacArthur Foundation; RO1
Keywords: Inflammation, Metabolism, Early Life Adversity, Body Mass Index, Adolescents

S45. Early Community-Based Services and Trajectories of Behavioral Problems Among Children With Varying Levels of Inattention/Hyperactivity-Impulsivity

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Background: Randomized controlled trials provide evidence for medications and behavior modification to treat Attention-Deficit/Hyperactivity Disorder (ADHD). However, few naturalistic studies have assessed the impact of early medication and school-based services on longitudinal changes in behavior.
Methods: Preschoolers (N=216) were recruited at 3-4 years old (T0): 140 had ≥6 inattentive and/or hyperactive symptoms; 76 had < 3 symptoms (ADHD status). Children's service use (ADHD Medication, behavioral counseling, Occupational, Physical and Speech therapy, and Special Educational Services; N=201) was assessed at 4-5 years (T1). Teachers rated behavior annually (T1-T7) using the BASC-2. Latent Class Analysis (LCA) was used to classify children based on their ADHD status and T1 services received. These classes were used as predictors in a longitudinal growth model of behavioral trajectories.
Results: Three groups emerged: Group 1 [N=116; Mean(SD) T1 ADHD symptoms=10.71 (9.99)] included children who were least likely to receive any treatment; Group 2 (N=60; Mean(SD) T1 ADHD symptoms=18.71 (11.17)] were most likely to receive school-based services; Group 3 (N=25; Mean(SD) T1 ADHD symptoms=30.25(8.97)] were most likely to receive medication and other services. Latent variable growth modeling showed that teacher-rated Inattention, Hyperactivity and Aggression were highest at T1 in Group 3 which also had a significantly greater decline in all behaviors than Group 1 and showed greater decrease in Aggression than Group 2. Rate of change was not different between Groups 1 and 2.
Conclusions: Behavioral improvements are greater among children who receive comprehensive, early services relative to those who do not.
Supported By: R01MH060698-07; NICHD SC2 HD086868
Keywords: ADHD, School-Based Services, Aggression, Medications, Developmental Trajectories

S46. Institutional Care is Associated With Changes in Brain Electrical Activity: Results From a Longitudinal, Randomized Control Trial of Children in Romania

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Background: Exposure to early psychosocial deprivation as a result of institutional care disrupts typical brain development. The Bucharest Early Intervention Project (BEIP) is the first longitudinal study to investigate the neurodevelopment of institutionalized infants randomized to foster care (FCG) versus care as usual (CAUG). Our previous work suggested that foster care placement, particularly before 24 months of age, significantly improved brain functioning compared to CAUG at 42 months and age 8. Here, we examined the brain electrical activity among the CAUG, FCG who were enrolled in the BEIP and never institutionalized (NIG) adolescents at age 16.
Methods: The sample included 112 adolescents from Bucharest, Romania (CAUG=37, F = 18; FCG=40, F = 21;

NIG=35, F = 23). Using a 64-electrode Hydrocel net, resting-state EEG was recorded alternating 1 minute of eyes open and eye closed for 6 minutes.
Results: Adolescents who had ever lived in institutions (CAUG + FCG) showed greater theta power compared to NIG, F(1,110)=4.17, p=.044. Results further revealed a timing effect of intervention, with an earlier timing of intervention linked to greater resting alpha, r=-.35, p<.02, and beta, r=-.30, p=.03, power within the foster care group.
Conclusions: Our findings suggest that the typical developmental shift of brain electrical activity from a dominance in lower frequency bands (e.g. theta power) to higher frequencies (e.g. alpha power) is altered in adolescents reared in institutions early in life. However, removing children from the institution and placing them into foster care earlier may facilitate the developmental shift of brain electrical activity.
Supported By: NIMH
Keywords: Neurodevelopment, EEG, Institutional Care, Brain Electrical Activity

S47. Early Life Traumatic Stressful Events are Associated With Increased Psychopathology and Poorer Cognitive Function in the Philadelphia Neurodevelopmental Cohort

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Background: Traumatic stressful events (TSE) during childhood and adolescence are established risk factors for psychopathology. The Philadelphia Neurodevelopmental Cohort (PNC) is an investigation of clinical and neurobehavioral phenotypes in a US community youth population.
Methods: PNC participants (N=9498, ages 8-21) underwent clinical interview-based assessment of psychopathology including TSE screening and computerized neurocognitive assessment. Linear regression analyses with TSE load as independent and 4 psychopathology factor scores was conducted. Binary logistic regression was used for dichotomous variables such as lifetime suicide ideation or cannabis use, controlling for covariates.
Results: Exposure to TSE was substantial (none, N=5204; one, N=2182; two, N=1092; three or more, N=830). Higher TSE load was associated with increased psychopathology in all clinical domains: psychosis, β=.384; mood-anxiety, β=.374; externalizing, β=.301; phobia, β=.261 (all betas, P=.000). Association of high TSE load was robust for suicidal ideation and cannabis use (OR compared to non-exposed 5.3 and 3.2, respectively, P=.000 for both). Among youths who experienced TSE (N=4294), experiencing TSE at age 12 or younger, or experiencing assaultive trauma (badly beaten, threatened with a weapon or sexually forced) was associated with worst psychopathology. TSE load was negatively associated with specific domains of cognitive performance efficiency including executive function, abstract reasoning and social cognition, but not with episodic memory.
Conclusions: Stress exposure is highly associated with various psychopathology domains, beyond PTSD and depression, and with poorer cognition, in a community, non-help-seeking youth population. The results highlight the importance of evaluating TSE load in community and clinical settings and of developing interventions that address youth TSE exposure.
Supported By: This work was supported by NIH grant MH-107235, MH-089983, MH-096891, MH-P50MH06891, the Dowshen Neuroscience fund, and the Lifespan Brain Institute of Children's Hospital of Philadelphia and Penn Medicine, University of Pennsylvania.
Keywords: Developmental Psychopathology, Stress, Adverse Childhood Experiences, Child and Adolescent Psychiatry

S48. Effects of a Single 10 Mg Dose of Methylphenidate on Attention Components and Executive Functions in Adults With ADHD

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Background: Methylphenidate (MPH) is a first line treatment option for attention-deficit/ hyperactivity disorder (ADHD). The aim of this pilot study was to assess the neuropsychological effects of a single low dose of MPH (10 mg orally) on different attention components and executive functions by using the computerized attention assessment battery TAP 2.3 (Test-batterie zur Aufmerksamkeitsprüfung).
Methods: Ninety-seven ADHD stimulant drug-naive DSM-IV adult ADHD patients were enrolled into this study. Neuropsychological evaluations were performed at baseline (BL), two weeks later following administration of a single oral 10 mg dose of MPH ("MPH test"), and 6 months after chronic MPH treatment with an adequate dose.
Results: Compared with BL, a single dose of MPH resulted in a statistically significant improvement in working memory performance, visual scanning, phasic and selective attention, sustained attention as well as executive functions in terms of number of mistakes and omissions (all p<0.0004). Reaction times were also significantly decreased in most of these tasks (p<0,005). Significant effects (p<0.001) were observed regarding the subjective assessments (patients felt more alert and calmer). These improvements on cognitive functions and subjective feelings were still observed after 6 months of MPH treatment.
Conclusions: Our results demonstrated that adult patients with ADHD are impaired in a variety of attention components and executive functions. Acute and chronic MPH administration enhanced significantly these functions. Thus, the "MPH test" would be useful in predicting subsequent response to MPH treatment in ADHD adult patients. Controlled prospective studies are needed to confirm this hypothesis.
Keywords: Adults ADHD, Methylphenidate, Neuropsychology, Testbatterie zur Aufmerksamkeitsprüfung

S49. Effects of a Single Dose of Methylphenidate on Saccadic Eye Movements in Adults With Attention-Deficit/Hyperactivity Disorder (ADHD)

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Background: Oculomotor tasks have been used to investigate executive functions and frontal-striatal functioning in humans, but there are relatively few studies on saccadic eye movements (SEMs) in adults with attention-deficit/hyperactivity disorder (ADHD). Methylphenidate (MPH) is an effective treatment for ADHD symptoms. We therefore evaluated SEMs before and after administration of a single MPH dose.
Methods: Forty stimulant drug-naive DSM-5 adult ADHD patients participated in this study. Saccade parameters were measured in the morning at baseline, and two weeks later following a single low dose administration of MPH (10 mg orally). Results were compared with 34 healthy control (HC) subjects. Oculomotor performances were determined in automatic attentional tasks (visually-guided-saccades, i.e. gap and step tasks) and voluntary attentional tasks (overlap and antisaccade tasks).
Results: Compared to HCs, ADHDs at baseline showed increased saccade latency (in the gap and antisaccade tasks; both $p< p<0.05$), increased directional errors in the antisaccade task ($p<0.005$), decreased average speed (in all tasks; $p<0.05$), decreased saccade accuracy (in all tasks), increased percentage of anticipatory saccades (in all tasks; all $p<0.001$) and increased percentage of express saccades (in the overlap task; $p<0.001$). A single low dose of MPH normalized the saccade latencies and the percentage of errors in the antisaccade task, and improved average speed (in automatic attentional tasks only).
Conclusions: Medication-naive ADHD adults show impairments on motor planning and response inhibition. A single-dose of MPH improves oculomotor performances in these patients. Thus, SEMs could be a potent pathophysiologic marker of deficits in frontal-striatal pathways in adults with ADHD.
Keywords: ADHD, Adults, Saccade, Antisaccade, Methylphenidate

S50. Modeling Neuronal Networks Using Patient-Derived Induced Pluripotent Stem Cells

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Background: Functional aberrations in neural circuitry have been associated with psychiatric disorders but little is known about how genetic risk could impact the coordinated activity of human neurons. Although animal models allow us to observe behavioral consequences related to genetic perturbations of neural circuits, complementary humanized models are needed to dissect cellular mechanisms that may contribute to emergent pathology using disease-relevant subtypes of human neurons.
Methods: Using human induced pluripotent stem cell lines from family members with and without a genetic risk factor for psychiatric disorders, we developed targeted differentiation protocols to generate enriched populations of both forebrain glutamatergic neurons and MGE-like GABAergic neurons. We then co-cultured these populations to evaluate network activity through extracellular recordings in a multi-well microelectrode array. By manipulating whether each cell type within the mixed culture carried the genetic risk factor, we were able to observe population-level interactions and the cell-type specific impact on overall network activity.
Results: Our initial results suggest that inclusion of the patient-derived population of GABAergic neurons decreased the coordinated activity of neighboring neurons recorded from individual electrodes, as well as spatially distributed neurons across the entire electrode array. In contrast, introducing glutamatergic neurons harboring the genetic risk factor seemed to have a larger impact on overall activity by decreasing the firing rate across the population.
Conclusions: The ability to generate renewable sources of human neurons allows us to probe how genetic and environmental risk factors may dysregulate functional properties of neurons in a cell-type specific manner, which may reveal mechanisms underlying circuit-level dysfunction.
Supported By: NIMH 7U19MH106434-02
Keywords: iPSC Model, Reprogrammed Cell Models, Electrophysiology, Psychiatric Disorders, Multi-Electrode Arrays

S51. Correlation of Gender With Risk for Mental Health Disorders and Exposure to Trauma in Adolescent Population With Mental Health Illnesses

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Background: Psychiatric risk assessment in the adolescent patient population plays a vital role towards obtaining better overall outcomes. Gender differentiation in individual risk factors have demonstrated significant results in the past thereby necessitating a comprehensive approach to risk assessment, which this study aims to evaluate.
Methods: Data was gathered from patients admitted in child psychiatric unit for any mental health illness. Patients aged 11-17 years (mean age 15.19 ± 1.56 years) were administered the Qualtrics survey within 48 hours of admission. Survey questions incorporated Morisky Medication Adherence Scale4, Screen for Child Anxiety Related Disorders, Strengths and Difficulties Questionnaire, Childhood Trauma Questionnaire, Child and Adolescent Mindfulness Measure, Pediatric Quality of Life Inventory and DSM-5 cross cutting symptom measures. Linear and logistic regression models of STATA were used for data analysis ($n=99$), and the sample was predominantly

female gender (n=62, 62.63%) and Hispanic-Latino race (n=45, 45.45%).
Results: Males were at higher risk for physical trauma (OR=1.17, CI=1.01-1.34, p=0.037); high risk for mania (β=0.133, p=0.03), low risk for conduct disorder (OR=0.29, CI=0.84-0.98 p=0.047), and low risk for hyperactivity (OR=0.24, CI=0.59-0.96, p=0.04), while females were positively correlated with sexual trauma (β=0.29, p=0.004). Physical functioning was almost equal in both genders (OR=1.01, CI=1-1.01, p=0.02).
Conclusions: Males were at higher risk for physical trauma (OR=1.17, CI=1.01-1.34, p=0.037); high risk for mania (β=0.133, p=0.03), low risk for conduct disorder (OR=0.29, CI=0.84-0.98 p=0.047), and low risk for hyperactivity (OR=0.24, CI=0.59-0.96, p=0.04), while females were positively correlated with sexual trauma (β=0.29, p=0.004). Physical functioning was almost equal in both genders (OR=1.01, CI=1-1.01, p=0.02).
Keywords: Child and Adolescent Psychiatry, Gender Differences, Mania, Childhood Trauma, Risk Assessment

S52. Optogenetic Interrogation of Prefrontal-Amygdala Synaptic Development

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Background: Early life experiences critically define cognitive and mental health function throughout life. Childhood and adolescence are the predominant age of onset for the majority of mental disorders, periods in which key brain areas involved in emotional processing, such as medial prefrontal cortex (mPFC) and amygdala, are maturing. Anatomical and morphological changes occur in both these areas during early life; nevertheless, how these changes affect circuit function and its consequences to the onset of mental illness is currently unknown.
Methods: We infused AAV virus expressing channelrhodopsin (ChR2) into the mPFC of C57BL6/J mice at postnatal day (P) 10, 15, 21, 30, 45 and 60, corresponding to infant, early and late juvenile, adolescent, late adolescent and adult developmental stages, respectively. Seven days after infection, brains were processed for patch clamp electrophysiology to record from basal amygdala principal neurons while selectively activating mPFC terminals by pulsing blue light.
Results: We found that mPFC projections arrive in amygdala at around P15, coinciding with an in amygdala spontaneous synaptic drive. Continuing through adolescence, mPFC-BLA circuits present pre- and postsynaptic strengthening as well as a transient enhancement in feedforward inhibition.
Conclusions: The profile and timing of our data are indicative of a developmental sensitive period in the mPFC-Amygdala pathway taking place between the juvenile and adolescent stages, during which synaptic transmission may be especially sensitive to adverse experience. Understanding how brain circuits implicated in mental illness mature will be critical for gaining insight into the etiology of those disorders, a necessary step for designing more targeted and efficient therapies.
Supported By: This work was supported by National Institutes of Health Grant MH105414 to R.L.C., the Brain and Behavior Foundation to R.L.C., and Human Frontiers Science Program Fellowship LT000191/2014-L to M.A.-C.
Keywords: Prefrontal Cortex, Amygdala, Developing Brain, Optogenetics, Electrophysiology

S53. Combined Resting State fMRI and EEG Investigation of Irritability

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Background: Irritability symptoms are an important dimension of Oppositional Defiant Disorder (ODD) that often persist through adolescence and are associated with increased risk for depression and anxiety into adulthood. Yet the neurobiology associated with the irritability dimension of ODD is poorly understood. Initial fMRI evidence provides support for differences in functional connectivity related to deficits in cognitive control and emotional liability, yet results have differed across tasks and previous studies have not sufficiently distinguish between specific disruptive behavior disorders or subtypes of behavioral problems. Resting State Functional Connectivity (RSFC) provides a basis for investigating the neural basis of activity in brain regions of interest (ROIs) independent of task stimulation.
Methods: Twenty college-aged participants underwent simultaneous EEG-fMRI scans including resting-state. MRI data were preprocessed using AFNI and bandpassed and censored as part of a multiple regression analysis to control for artifacts and motion. Whole-brain Resting State Functional Connectivity (RSFC) was assessed using ALFF. EEG data were preprocessed and analyzed using NetStation and FieldTrip.
Results: Irritability symptoms were significantly correlated within several ROIs that comprise the default mode network. There was a significant between-group difference (based on depression scores) in ALFF levels in the right insula and anterior cingulate. EEG findings support significant differences in beta and alpha amplitude.
Conclusions: These results are consistent with previous fMRI findings related to task-based differences. They suggest that RSFC associated with irritability may be distinct from affective components of the disorder. Further investigations across development are needed to better characterize the pathophysiology associated with chronic irritability.
Keywords: Irritability, Resting State fMRI, Electroencephalography (EEG), Conduct Disorder, Default Mode Network

S54. Exploring the Neurophysiological Correlates of Early and Late Emotional Interference on Response Preparation in Youth With Bipolar Disorder

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Background: Emotional dysregulation in pediatric bipolar disorder (pBD) can affect attentional processes, which are influenced by response preparation. However, the temporal dynamics of emotional interference on response preparation in pBD is poorly evaluated. Our aim is to explore P100 and LPP amplitudes during response preparation processes with emotional distractors in patients with pBP and healthy controls (HC).
Methods: Enrolled were 7- to 17- year-old subjects with pBP (N=13) and healthy controls (HC) (N=12). Subjects passively viewed fearful, neutral and happy faces on a green, red or blank background. Subjects were required to perform a cognitive task cued by green and red backgrounds, whereas no action was required after viewing the blank screen. P100 was recorded between 70ms and 140ms, whereas LPP was recorded between 300 and 1000ms. Effects were explored with general linear models.
Results: We found a color*group interaction (p=0.12). Post-hoc analyses revealed that only in patients, the blank background elicited greater P100 amplitude than both red (p=0.064; Cohen's D=0.654) and green background (p=0.088; Cohen's D=0.499), irrespective of the emotional face. We explored also a trend level significant emotion*group interaction (p=0.06). Post-hoc analyses revealed that happy faces elicited greater P100 amplitude than fearful faces (p=0.01; Cohen's D=0.246), irrespective of the background. As regard the P100 peak latency, both green and red backgrounds elicited a later peak than blank background (p=0.029; Cohen's D=0.733 and p=0.019; Cohen's D=0.850, respectively).
Conclusions: Youth with pBP demonstrate poor early attentional visual processing, possibly due to an interference from emotional stimuli to the available attentional resources.
Supported By: Dunn Foundation
Keywords: Emotion Regulation, Neurophysiology, Pediatric Bipolar Disorder, Emotional Face Processing

S55. Neural Responses to Reward in Childhood Predict Stress Reactivity in Early Adolescence

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Background: Altered responses to both reward and acute stress are a well-known risk factor for psychiatric disorders, including depression and anxiety. Whereas some studies have examined changes in neural reward processing under or after stress conditions, few studies have tested whether such responses are related to stress reactivity later in life, especially in sensitive developmental periods such as early adolescence.
Methods: Thirty-four participants, twenty females, performed a reward processing task during fMRI at age 10 (M=10.5, SD=0.4), and then a version of the Trier Social Stress Test (TSST) at age 13 (M=13.2, SD=0.6). Multiple linear regression analysis tested whether changes in BOLD signal during reward anticipation, and encoding of reward prediction error (RPE) during reward feedback, predicted both observer- and self-reported stress reactivity three years later.
Results: During reward anticipation, lower left ventral caudate response was associated with higher self-reported stress in the TSST three years later (β=-0.37, p=0.037), whereas lower insula response was associated with higher observer-reported stress (β=-0.56, p=0.001). Stronger RPE signals encodings in the right ventral caudate and cingulate cortex were associated with higher self- (β=0.40, p=0.025) and observer-reported stress (β=0.39, p=0.025), respectively.
Conclusions: Diminished ability to foresee positive outcomes as a consequence of one's performance, highlighted by lower anticipation and higher sensitivity to such outcomes when these happen unexpectedly, might increase anticipatory anxiety when facing challenging situations. On the other hand, stronger RPE signals might also facilitate positive learning under conditions of treatment exposure to aversive situations.
Supported By: NIMH Intramural Research Program
Keywords: Reward, fMRI, Stress Reactivity, Trier Social Stress Test, Children and Adolescence

S56. The Neural Correlates of Frustration in Youth With Disruptive Behavior Disorders

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Background: Disruptive Behavior Disorders (DBD) are a major mental and public health concern. Youth with DBDs show heightened levels of aggression, including reactive aggression (i.e., aggression in response to threat, social provocation or frustration). There have been claims that youth with DBDs have a low frustration tolerance. However, the neural correlates of frustration have not been examined in this population.
Methods: Sixty youth with DBDs and 39 Typically Developing (TD) youth aged 10 to 18 years, undergoing functional MRI, completed a frustration task (Yu et al., 2014) where they worked towards a rewarded goal but could be randomly blocked from achieving this goal.
Results: Relative to the TD youth, youth with DBDs exhibited stronger activation in both left ventral striatum and dorsal anterior cingulate cortex to outcome regardless of whether the participant's goal was blocked or achieved. Moreover, within the youth with DBDs, a conduct problems severity-by-outcome interaction emerged in bilateral ventral striatum. Conduct problems severity was positively associated with greater differential responses to blocked relative to achieved goals.
Conclusions: Youth with DBDs showed increased ventral striatum and dorsal anterior cingulate responses in response to frustration induction. Moreover, the degree to which participants with DBDs showed a differential response to blocked

relative to achieved goals positively related to their severity of conduct problems. It is possible that an increased risk for reactive, antisocial behavior may at least partially reflect a heightened sensitivity to the receipt of reinforcement associated with goal achievement.
Supported By: Boys Town National Research Hospital, National Institute of all Mental Health
Keywords: Frustration, Disruptive Behavior Disorders, Reward Processing

S57. Insulin-Like Growth Factor Expression in Postmortem Autistic Anterior Cingulate Cortex

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Background: Two hallmark pathophysiological features of autism spectrum disorder (ASD) are increased brain size and peripheral inflammatory abnormalities. We hypothesize that peripheral inflammatory processes in ASD lead to activation of central inflammatory events that activate microglia and astrocytes, deleteriously affecting synapses and neural signaling pathways that are required for normal social behavior. The current study examined inflammatory markers in the anterior cingulate cortex (ACC) in ASD.
Methods: Quantitative PCR was used to investigate gene expression levels of inflammatory molecules including IL1β, CD68, HLA-DRA, NOS2, MRC2, and insulin-like growth factor 1 (IGF1), in ACC punch-dissected tissue from ASD and typically developing (TD) control donors. Gene expression levels were examined in gray (N=13) and white matter (N=10) tissue homogenates. Gene expression levels of the IGF1 receptor (IGF1R) were measured in pyramidal neurons laser captured from ACC layer III (N=3).
Results: In ASD donors, gene expression of IGF1 was significantly increased in ACC white matter homogenates when compared to TD control tissue (p=0.013). Other inflammatory gene expressions were not significantly different comparing ASD to TD control donors. While IGF1R gene expression levels were similar in ACC homogenates from ASD and TD donors, laser-captured pyramidal neurons from the ACC demonstrated robustly elevated IGF1R gene expression levels in ASD (p=.004).
Conclusions: IGF1 released from activated microglia can activate downstream signaling pathways in pyramidal neurons that are critical to synaptic formation, plasticity and maintenance. IGF1 signaling through the IGF1R may be increased in ASD, providing a potential etiology for increased brain size and dendritic arborization in ASD.
Supported By: East Tennessee State University
Keywords: Pyramidal Neurons, Growth Factors, Autism, Cingulate Cortex

S58. Functional Characterization of Brain Organoids Derived From Human Pluripotent Stem Cells

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Background: Aberrant gamma-aminobutyric acid (GABA) system, the major inhibitory neurotransmitter in the CNS, is highly implicated in autism spectrum disorder (ASD). Development of the GABAergic neurons in human has only been recently examined, and the results unexpectedly show that GABA neurons are overproduced in ASD (Mariani et al 2015). It is essentially unknown as to how GABAergic transmission is perturbed in developing ASD circuitry.
Methods: Subject selection was based on DSM-IV diagnosis with ASD or Pervasive Developmental Disorder (NOS). Skin biopsy was collected from patients (n=4) and their biological parents (n=4) recruited from the Yale Child Study Center Autism Program. Fibroblasts that are terminally were differentiated back to pluripotent stem cells (iPSCs) allows the investigation of human neurodevelopment in vitro. The iPSCs are developed into three-dimensional organoids that resemble human brain tissue. Immunocytochemistry was used to detect bio-markers that express correspondingly to different neurodevelopmental stages. Electrophysiology was used to characterize functional analysis of membrane properties and excitability.
Results: Preliminary study here show that our organoids (1) have neuronal differentiation potential with cortical cell type-specific markers, and (2) display functional voltage-gated channels and neuronal excitability, as shown having robust inward currents were detected at post-terminal differentiation day (TD) 10-20 (0.37±0.1nA) and at TD 30-50 (6.8±1.4nA, n=18, p<0.001). These cells also show action potential with threshold -40±5.2mV, n=15
Conclusions: Future studies will use electrophysiology and imaging techniques to make direct comparison on excitatory and inhibitory synaptic events between control and autism groups, and will elucidate the underlying cellular and molecular mechanisms.
Supported By: NARSAD
Keywords: Brain Organoids, Autism Spectrum Disorder, Electrophysiology

S59. Alpha-7 Nicotinic Acetylcholine Receptor Positive Allosteric Modulator Galantamine in Autism Spectrum Disorder

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Background: The alpha-7 nicotinic acetylcholine receptor (a7nAChR) has been implicated in the pathogenesis of neurodevelopmental disorders and specifically in Autism Spectrum Disorder (ASD). a7nAChRs are predominantly expressed on inhibitory neurons of the hippocampus and thalamic reticular nuclei, and a physiological correlate, the inability to inhibit the response to sensory stimuli, has been identified as a key neurobiological deficit in ASD. Molecular evidence indicates a deficiency of a7nAChR expression in ASD.
Methods: We propose a clinical translational target engagement study as a first step to develop galantamine in childhood ASD. 18 children with ASD will be enrolled in our planned

placebo-controlled, randomized, three-arm, single dose challenge Phase 1b study. A gene-first methodology will be used to enrich for subjects with the 15q13.3 deletion syndrome, which negatively affects a7nAChR expression. Subjects will three challenge treatments (galantamine 12 mg, galantamine 24mg or placebo) at separate visits. Diagnosis will use DSM-5 criteria, the ADOS-2, ADI-R, Stanford-Binet Intelligence Scales and medical history to ensure population homogeneity and enhanced signal detection.
Results: Target engagement will be assessed using a P50 inhibitory paradigm, with additional assessments (RBANS, ABC-I, RBS-R, ASR-R, CGI-I) to be performed for correlation with electrophysiologic findings.
Conclusions: Individuals with ASD often have associated comorbidities that impact behaviors, development and caregiver burden. Approved treatments target disruptive behaviors but have a high side effect profile. Novel treatments for core features of the disorder with a lower side effect profile are needed. Previous studies of treatments that act on the GABAergic system and nicotinic receptors in ASD have demonstrated potential efficacy.
Keywords: Autism Spectrum Disorder, Galantamine, Alpha-7 Nicotinic Acetylcholine Receptor

S60. The Sensory Domain as a Target for Treatment in ASD Clinical Trials: Electrophysiological and Behavioral Markers of Therapeutic Change

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Background: Sensory symptoms represent a core feature of autism spectrum disorder (ASD) and a novel domain to develop outcome measures for clinical trials. This study piloted the utility of electrophysiological and behavioral measures for assessing change in sensory reactivity during a clinical trial of insulin-like growth factor-1 (IGF-1) in children with Phelan-McDermid syndrome (PMS). PMS is one of the most common single-gene causes of ASD and sensory hyporeactivity is a prominent feature of the syndrome.
Methods: Participants included six children with PMS 5-12 years of age enrolled in an ongoing placebo-controlled, double-blind, crossover design study. Transient visual evoked potentials (VEPs) and the Sensory Assessment for Neurodevelopmental Disorders (SAND) were collected at baseline and week 12 during Phase I and Phase II. VEPs reflect the sum of excitatory and inhibitory postsynaptic potentials and provide a window into the brain to examine excitatory/inhibitory balance. The magnitude squared coherence statistic (MSC) was used to examine coherence of high-frequency oscillatory responses. The SAND is a clinician-administered observation and corresponding caregiver interview that quantifies sensory reactivity according to DSM-5 criteria for ASD (hyporeactivity, hyperreactivity, seeking).
Results: There was a significant increase in low gamma (30-36 Hz) activity following IGF-1 relative to baseline ($p=.048$). Notably, MSC increased in 5 of 6 patients. Significant clinical improvement was observed on the SAND Hyporeactivity Domain following IGF-1 treatment ($p=.037$).
Conclusions: Our results suggest that VEPs and the SAND represent two novel outcome measures for use in clinical trials for individuals with ASD and related conditions.
Supported By: R21
Keywords: Autism Spectrum Disorder, Visual Evoked Potential, Sensory Reactivity, Clinical Trial, Phelan-McDermid Syndrome

S61. Correlation of Age to Psychotropic Medication Adherence and Substance Abuse in Adolescents With Mental Health Illnesses

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Background: Positive mental health outcomes in adolescents are associated with adherence to prescribed psychotropic medication regimen and avoidance of substance abuse. The existing literature has no consensus on the association of age and psychotropic medication adherence in adolescents. Substance abuse is more common in older adolescents than in younger adolescents. This study aimed to assess the correlation of age with risk factors for adolescent with mental health illnesses.
Methods: Data was obtained from assenting admitted inpatients aged 11-17 years (mean age 15.19 ± 1.56 years) administered within 48 hours of admission using Qualtrics survey composed from questions from the Morisky Medication Adherence Scales, Screen for Child Anxiety Related Disorders, Strengths and Difficulties Questionnaire, Childhood Trauma Questionnaire, Child and Adolescent Mindfulness Measure, Pediatric Quality of Life Inventory, and DSM-5 cross cutting symptom measures. Analysis of 99 observations was performed using linear and logistic regression model in STATA. The sample was predominantly female ($n=62$, 62.63%) and Hispanic-Latino race ($n=45$, 45.45%).
Results: Age was positively correlated with adherence ($\beta=0.01$; $p=0.001$), risk for substance abuse (OR=1.65; CI=1.22-2.24; $p=0.001$) and was negatively correlated with current medication use ($n=51$, $\beta=-0.58$, $p<0.001$).
Conclusions: Medication adherence and risk of substance abuse increases with age. This study's findings reconcile with the literature regarding age and substance abuse and provide another example for the currently unclear association between age and psychotropic medication adherence in adolescents.
Keywords: Adolescence, Non-Adherence, Substance Abuse, Treatment Outcomes

S62. Neurotransmitter-Wide Association Study of Prenatal Exposure to Medication With Autism Spectrum Disorder

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Background: Prenatal exposure to certain medications has been hypothesized to influence the risk of autism spectrum disorder (ASD). However, safety of the majority of pharmaceuticals has not been verified. We investigated the effects of all medications acting on the major neurotransmitter systems, and taken by pregnant women in our sample, on the risk of ASD in offspring.
Methods: This is a case-cohort study using prescription data from Israel (nASD=1,405, ncontrols=94,573). Using publicly available bioinformatics tools, we identified 55 groups of medications affecting neurotransmitter-relevant drug targets prescribed to pregnant women in our sample. We investigated the effects of exposure to those groups using Cox proportional hazard regression, controlling for sampling probability and family structure, and adjusting for the relevant confounders.
Results: After quality control, we tested 34 groups of medications, 26 of which showed no association with ASD. After adjustments, we observed higher rates of ASD among children prenatally exposed to antagonists of neuronal acetylcholine α receptor (HR=18.20 (1.76-188.00), p=0.02) or GABA transaminase inhibitors (HR=3.23 (0.82-12.73), p=0.09), and decreased rates among those exposed to cannabinoid receptor agonists (HR=0.74 (0.56-0.97), p=0.03), muscarinic receptor 2 agonists (HR=0.49 (0.24-0.97), p=0.04), opioid receptor κ and ε agonists (HR=0.67 (0.45-0.99), p<0.05), or adrenergic receptor α 2C agonists (HR=0.44 (0.20-0.99), p<0.05). Significant effects of serotonin reuptake inhibitors and agonists of adrenergic receptor α 1A were not observed after the final adjustments.
Conclusions: In this population the majority of the associations between maternal medication use and offspring ASD are likely not due to effects on known pharmacological targets of those medications.
Supported By: Seaver Foundation
Keywords: Pharmacoepidemiology, Neurodevelopment, Autism, Epidemiology, Pregnancy

S63. Relationship Between Problematic Internet Use and Tobacco Smoking in Adolescents

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Background: Problematic Internet use (PIU) is associated with substance use in adolescents. Tobacco smoking often starts in adolescence and nicotine is hypothesized to be a gateway drug to other substances. Thus, the relationship between PIU and tobacco smoking is of interest.
Methods: PubMed, PsycINFO and Web of Science were searched from inception through June 2017. The search terms PIU, Internet addiction, pathological Internet use, and excessive Internet use were combined with key words smoking, cigarettes, nicotine, and tobacco. Inclusion criteria were studies in English, sample size > 200 subjects, mean subject age of 18 years or less, and sufficient data to calculate pooled odds ratios and effect sizes.
Results: 8 cross-sectional studies with 197,680 unique subjects, including 12,197 (6%) with PIU, met inclusion criteria. Studies were from Europe (n=4), Asia (n=3), and the United States (n=1). PIU and smoking history were assessed by self-report. Six different PIU measures with defined criteria were used. Studies presented data on tobacco use as current (n=2), lifetime (n=3), or both (n=3). PIU had a positive relationship with four (80%) of the current smoking and six (100%) of the lifetime smoking studies. Analyses demonstrated a significant relationship between PIU and current (OR=1.86, 95%CI 1.48-2.33, z=5.378, p<.001) and lifetime (OR=1.93, 95% CI=1.84-2.03, z=26.58, p <.001) smoking.
Conclusions: Although methodologies varied between studies, most found a positive association between PIU and both current and lifetime tobacco smoking. Longitudinal studies are needed to determine direction of causality and risk for use of additional substances.
Keywords: Problematic Internet Use, Tobacco, Cigarette Smoking, Adolescents

S64. Autonomic Nervous System Function and Emotion Regulation in Adolescent Non-Suicidal Self-Injury

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Background: Non-suicidal self-injury (NSSI) and borderline personality disorder (BPD) are associated with difficulties in emotion regulation that haven been shown to be related to autonomic nervous system (ANS) function. Research on ANS function in NSSI and BPD, however, predominantly exists in adults and evidence in adolescents is scarce.
Methods: The presentation draws on data collected in a series of studies including predominantly female adolescents (12-17 years) fulfilling DSM-5 diagnostic criteria for NSSI and/or BPD. ANS activity was quantified by ambulatory recordings of heart rate (HR) and its variability (HRV). Different facets of emotion regulation were quantified using structured interviews, self-reports and ecological momentary assessment.
Results: In adolescents with NSSI (n=30) both HR r=.479, p=.007) and HRV (r=−.418, p=.022) were associated with the number of BPD criteria endorsed. Findings for HR (r=.359, p=.040) and HRV (r=-.510, p=.002) replicated in an independent clinical sample of n = 33 adolescents with NSSI. In a 1-year longitudinal follow-up (n=18), change in HRV (r=-.516, p=.033) and HR (r=.532, p=.028) were correlated with trajectories in BPD severity, such that improvements in BPD severity were associated with increased HRV and decreased HR. The talk will cover additional data on different facets of emotion

regulation in association with ANS function, treatment related changes and potential underlying mechanism (i.e. catecholamines).
Conclusions: Altered ANS function provides a psychophysiological mechanism underlying difficulties in emotion regulation in adolescent NSSI. Measures of HRV in the study of developmental psychopathology may guide psychiatric assessment and the monitoring of treatment outcome.
Keywords: Adolescence, Non-Suicidal Self-Injury, Borderline Personality Disorder, Heart Rate Variability

S65. High Temporal Resolution Event-Related Functional Spectroscopy Reveals Grossly Abnormal Neurotransmitter Responses in Pontine Reticular Nuclei in Autism Spectrum Disorder

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Background: Atypical excitation:inhibition has been posited as a core deficit of autism spectrum disorder (ASD). To test this in the amygdala, we previously adapted functional magnetic resonance spectroscopy to an event-related design with high temporal resolution (ht-fMRS). We found an inverted or delayed glutamate response and a relation between higher glutamate:GABA and more severe social impairments. In parallel, our previous work mapped autistic social impairments onto quantitative measures of motor behavior. The microstructural abnormality in the medial pons mediated this relationship. We designed the current study to investigate excitation:inhibition in the pons with a motor-specific ht-fMRS paradigm.
Methods: In the pons-focused ht-fMRS task (modeled after the amgydala task), participants used bilateral, MRI-compatible grip strength responders to indicate neutral (hard grip) or emotional (light grip) faces (intertrial interval = 3s).
Results: Control participants (3 typically-developing and 3 ADHD) showed an expected GABAergic response that rose during the 3s stimulus presentation and recovered in 1.5s after stimulus offset in the emotion-light grip condition. The neutral-hard grip condition evoked a lessor GABAergic response and a sustained glutamate elevation, similar to the amygdala glutamate response. The autism group (9 participants) showed no significant GABA response to either condition and a striking opposite glutamate deflection from controls that is evident in both conditions.
Conclusions: Consistent with amygdala findings, grossly inverted glutamate responses, measurable with high-temporal resolution fMRS, are evident in pontine motor regions, including regions mediating emotion-modulated startle, and may be a broad subcortical or global abnormality in ASD. Future analyses will include counterbalanced conditions (neutral-light-grip and emotional-hard-grip).
Supported By: The Hartwell Foundation's Individual Biomedical Award (Travers, PI)
Keywords: Magnetic Resonance Spectroscopy, Functional Imaging, Autism, Development, Biomarker

S66. A Clinical Trial Investigating the Safety and Tolerability of Floatation-Rest in Anorexia Nervosa

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Background: Floatation-REST (Reduced Environmental Stimulation Therapy), a novel body-based intervention which attenuates exteroceptive sensory input to the nervous system, is being increasingly utilized as a non-pharmacological tool for reducing anxiety and stress. Anorexia nervosa (AN) is characterized by heightened anxiety, distorted body image, and disrupted interoception, raising the question of whether Floatation-REST might positively impact these symptoms, but there are no studies documenting the safety or tolerability of this procedure.
Methods: This open-label study (clinicaltrials.gov: NCT02801084) examined the physiological and subjective effects of Floatation-REST in weight-restored outpatients with AN. The primary aim was to evaluate the safety and tolerability of this intervention across four float sessions. Orthostatic blood pressure was measured after each session (primary outcome) using a wireless waterproof system. Participants also rated their affective state, body image, and interoceptive sensations before and after each session (exploratory outcomes).
Results: Twenty-one AN patients completed the study (average EDE-Q: 2.3+/-1.4, average BMI 22+/-2.7. Primary outcome: there was no evidence of systolic or diastolic orthostatic hypotension after each float in any participant, and no adverse events. We observed significant improvements in anxiety ($p<0.001$, Cohen's $d>1$), negative affect ($p<0.01$, Cohen's $d>0.5$), heightened interoceptive awareness for cardiorespiratory ($p<0.01$, Cohen's d 0.2-0.5) but not gastrointestinal sensations, and reduced body dissatisfaction ratings ($p<0.001$, Cohen's $d>0.5$) following floating.
Conclusions: The findings from this initial trial suggest that individuals with AN can safely tolerate the Floatation-REST environment. The observed improvement in affect and body image disturbance suggests that this intervention might be investigated for potential clinical benefit in more acutely ill patients.
Supported By: The William K. Warren Foundation
Keywords: Anorexia Nervosa, Anxiety, Interoception, Body Image Disturbance, Negative Affect

S67. Biomarker Change During Inpatient Treatment for Anorexia Nervosa and Associations With Weight Outcomes

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Background: Anorexia nervosa (AN) is characterized by extreme food restriction, resulting in a body weight that is less then minimally expected. Building on the link between AN and HPA-axis hyperactivity and results showing that AN shares a genetic etiology with metabolic factors, we examined the stability and change of related-biomarkers during weight restoration and associations with weight change and weight.
Methods: Women receiving inpatient treatment for AN (n=46) were assessed at admission (T1), discharge (T2), and 3-months post-discharge (T3). Fasting, morning blood samples were collected to assay biomarkers of physiological stress (cortisol, ACTH, norepinephrine [NE]) and metabolic markers (glucose, albumin, creatinine) at T1 and T2. Weight was assessed at each time point.
Results: Weight ($t = 7.6$, $p<.001$) and glucose ($t = 3.0$, $p<.05$) increased from T1 to T2 whereas creatinine decreased ($t = 4.2$, $p <.01$). No significant changes in cortisol, ACTH, or NE were observed with weight restoration. In regression models, change in ACTH ($B = .33$, $p<.05$) and glucose ($B = .50$, $p<.05$) from T1 to T2 predicted weight restoration (weight change from T1 to T2). Change in glucose ($B = -1.1$, $p< .05$) predicted weight at T3, but not weight change from T2 to T3.
Conclusions: Glucose change during weight restoration may be a relevant biomarker for predicting later weight outcomes in AN such that inpatients with a higher increase in glucose during weight restoration are at increased risk for a lower post-discharge weight. Markers of metabolic health could be useful biomarkers for monitoring and predicting treatment outcome.
Supported By: NIH K01MH106675
Keywords: Anorexia Nervosa, Eating Disorders, Serum Biomarker, HPA Axis, Metabolic

S68. Affective and Neurocognitive Dimensions in a Transdiagnostic Eating Disorder Sample: Examining Measurement Convergence and Associations With Clinical Symptoms

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Background: Eating disorders (EDs) are serious psychiatric illnesses with shared biobehavioral mechanisms. Consistent with dimensionally-oriented research initiatives (i.e., RDoC), the current data are drawn from an ongoing NIMH-funded K23 (MH101342) examining affective and neurocognitive processes underlying ED psychopathology.
Methods: A non-ED-specific sample was recruited, requiring clinically significant ED symptoms and ED-related impairment. Participants (N=50 women) completed well-validated clinical interviews, questionnaires, and behavioral/neurocognitive tasks. Bivariate correlations were computed to evaluate convergence across tasks and questionnaires assessing corresponding constructs, as well as associations with affective and ED symptoms.
Results: Behavioral and self-report measures converged for emotional reactivity (r=.30, p=.044), but not inhibition or reward processing. Anxiety symptoms were associated with task-based (r=.38, p=.007) and self-report (r=.43, p=.003) emotional reactivity, but only self-report inhibition (r=-.31, p=.031) and neither measure of reward processing. Depression symptoms were associated with task-based (r=.35, p=.013) and self-report (r=.32, p=.031) emotional reactivity, but not with inhibition or reward processing. For ED symptoms, binge eating was associated only with self-report inhibition (r=-.29, p=.046), restriction was associated only with self-report emotional reactivity (r=.31, p=.037), and purging demonstrated only a trend in relation to self-report reward processing (r=.28, p=.059).
Conclusions: Preliminary findings suggest the salience of affect and neurocognition in EDs, but also demonstrate discordance between actual performance and corresponding self-reported capabilities/experiences. This has implications for understanding ED onset, maintenance, and/or treatment. In particular, actual performance deficits would indicate certain potential neurobiological mechanisms and treatment approaches, whereas perceived difficulties in the absence of actual deficits may suggest the need to investigate and intervene on alternative targets.
Supported By: NIMH; K23MH101342
Keywords: Eating Disorders, Emotion, Neurocognition, Assessment, Research Domain Criteria (RDoC)

S69. Severity of Suicide Attempt is Associated With Epigenetic and Transcriptional Changes in the CYP2D6 Gene

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Background: To our knowledge, this is the first study investigating both epigenomics and transcriptomics in suicide severity in a cohort of suicide attempters.
Methods: We measured the genome-wide methylation pattern in whole blood using the Illumina Infinium Methylation EPIC BeadChip. Patients were stratified into one of two groups (high risk or low risk) based on the severity of the suicidal behaviour. Having used a violent suicide attempt method, scoring greater than 6 points on the Freeman suicide intention scale, and later suicide completion were considered as high risk. On the association analysis between DNA methylation and severity of suicide attempt, we included CpG sites whose methylation levels have been shown by Hannon et al. to have a high correlation between blood and brain. A total of 12,931 CpG-sites were included in the subsequent analysis. Next, we used open-access data (http://www.ebi.ac.uk/arrayexpress/experiments/E-GEOD-24095/) to investigate the expressional profile of detected candidate genes in postmortem brain samples of 11 matched MDD suicide cases and controls sampled from both the dentate gyrus and the CA1 subregions of the hippocampus.
Results: Cg07016288 - located 163 bp upstream of the transcription start site of the cytochrome P450 2D6 (CYP2D6) gene - was significantly hypomethylated in the high-risk group (bonferroni corr.). CYP2D6 was further demonstrated to be significantly hypoexpressed in post-mortem brain samples

from the dentate gyrus (p<10e-4) of MDD suicide cases compared to controls.
Conclusions: Our finding of epigenetic and transcriptional changes in CYP2D6 gene may be related to treatment resistant depression, a risk factor for suicide.
Keywords: Epigenetics, Suicide Severity Index, CYP2D6

S70. Endogenous Fluctuations in the Dopaminergic Midbrain Modulate Choice Behavior

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Background: Deficits in the dopaminergic reward pathways have been associated with gambling addiction as well as other psychiatric disorders where patients often co-present with problem gambling, such as Attention Deficit Hyperactivity Disorder (ADHD). While pharmacologically boosting dopamine increases risk-taking behavior, little is understood about whether endogenous fluctuations in dopaminergic brain areas can lead to momentary impulses that similarly influence choice behavior.

In the present study, we explore the effect of intrinsic fluctuations in the substantia nigra and ventral tegmental area (SN/VTA) complex on risk-taking behavior. The SN/VTA contains the highest concentration of dopaminergic neurons in the human brain.
Methods: We used real-time functional Magnetic Resonance Imaging (rtfMRI), combined with an individually calibrated probabilistic gambling task, to probe whether changes in baseline levels of BOLD (Blood Oxygenation Level-Dependent) activity in the SN/VTA predict subsequent risk-taking behavior in 43 participants. The use of rtfMRI here allowed us precise control over trial presentation across conditions.
Results: When SN/VTA activity was low, participants exhibited greater risk-taking behavior ($t42 = 3.76$, $p < 0.001$), and were also slower to make a decision ($t42 = 3.22$, $p = 0.003$). Computational modelling revealed that the difference in risk-taking between conditions was driven by an increased bias to gamble for any option presented, as opposed to a change in individual utility functions.
Conclusions: Our results suggest that endogenous fluctuations in SN/VTA BOLD activity modulate choice behavior, consistent with the possibility that low intrinsic dopamine may underlie impulsive behaviors in related psychiatric disorders.
Supported By: Wellcome Trust; Max Planck Society
Keywords: Dopamine, Ventral Tegmental Area, Risk Taking, Real-Time fMRI, Computational Modeling

S71. Urban Mind: Using Smartphone Technologies to Investigate the Impact of Nature on Mental Wellbeing in Real Time

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Background: It has been suggested that exposure to natural features within the urban environment can have beneficial effects on mental health. However, most existing evidence comes from studies that used a cross-sectional design and did not consider interactions with individual characteristics such as age, lifestyle and vulnerability to mental illness.
Methods: We developed a smartphone-based tool (Urban Mind; www.urbanmind.info) to examine how exposure to natural features affects momentary mental wellbeing in real-time and real-world environments and how this depends on individual characteristics. The Urban Mind tool was used to monitor 108 anonymous volunteers who completed a total of 3013 assessments over a one-week period. The data were analysed using random intercept models.
Results: Specific natural features such as being outdoors, seeing trees, hearing birdsong and seeing the sky, had beneficial effects on momentary mental wellbeing ($p < 0.001$). These associations were still evident up to 7.5 hours after a single exposure had taken place, indicating time-lasting benefits. In addition, these associations were stronger in people with higher trait impulsivity - a psychological measure of one's tendency to behave with little forethought or consideration of the consequences, and a predictor of higher risk of developing mental health issues.
Conclusions: Our investigation extends existing evidence on the benefit of nature on mental wellbeing, by demonstrating time-lasting effects that interact with an individual's vulnerability to mental health issues. These findings have potential implications both from the perspectives of global mental health and urban planning and design. We are currently trialing the Urban Mind app in clinical populations.
Supported By: This project was sponsored by the Engineering and Physical Sciences Research Council (EPSRC) via a grant from the Van Alen Institute and the Sustainable Society Network+.
Keywords: Nature, Mental Wellbeing, Mental Health, Mobile Health, Ecological Momentary Assessment

S72. The Association Between Aggression, Impulsivity, and Suicidal Behaviors in Female Compared to Male Veterans

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Background: Findings from the Office of Suicide Prevention (2016) suggest that suicide rates may be increasing disproportionately in female compared to male veterans. Previous studies have shown a wide array of variables associated with suicidal behaviors; however, prior research has focused predominantly on males. The current study sought to examine the association between aggression, impulsivity, and suicidal behaviors in female compared to male veterans.

Methods: Forty-six female and 156 male veterans completed a structured interview of lifetime suicidal ideation/attempts (i.e., suicidal behaviors, Columbia Suicide Severity Rating Scale) and self-report measures of aggression (Buss-Perry Aggression Questionnaire) and impulsivity (Barratt Impulsiveness Scale). ANOVAs were run to examine sex differences in demographic and clinical variables. Multiple regressions examined the association between impulsivity and aggression to suicidal behaviors by sex.
Results: ANOVA showed no significant sex differences on age, suicidal behaviors, or impulsivity; males reported higher aggression than females. For males, the overall regression model was significant with both aggression and impulsivity adding significantly to the prediction of suicidal behavior (overall model $F(2,154)=30.29$, $p<0.001$, $R2=0.28$). The overall model for females also was significant (overall model $F(2,44)=4.187$, $p=0.02$, $R2=0.16$). However, only impulsivity and not aggression added significantly to the prediction of suicidal behavior for females.
Conclusions: Results suggest that aggression and impulsivity contribute to suicidal behaviors in male veterans, whereas impulsivity contributes to suicidal behavior in female veterans. These findings have important clinical implications, as risk factors for suicidal behaviors in female and male veterans are likely to differ, suggesting critical differences in treatment foci by sex.
Supported By: MSRC, VA Merit Review, Salt Lake City MIRECC
Keywords: Sex Differences, Suicide, Veterans

S73. Effects of Dopamine and Serotonin Depletion on Reward and Aversion Processing

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Background: Reward and aversion processing abnormalities in disorders such as depression may be linked to decreased serotonin or dopamine function. However, the differential contributions of these neurotransmitters remain unclear. This study utilised tryptophan (TD) and tyrosine/phenylalanine (TPD) depletion to examine how lowered serotonin and dopamine levels, respectively, affect responses to pleasant and unpleasant stimuli.
Methods: In a double-blind design, 65 healthy volunteers were randomly allocated to the tryptophan depletion ($N=21$), tyrosine/phenylalanine depletion ($N=21$), or placebo ($N=23$) groups. Five hours after consumption of the depletion drink, participants completed a button pressing task during fMRI scanning as part of which they could win chocolate tastes or avoid aversive tastes with differing probabilities.
Results: ROI analyses revealed that, compared to placebo, TD increased insula responses significantly ($p=0.039$) and amygdala activation marginally ($p=0.066$) to cues indicating possible unpleasant taste receipt, and reduced insula responses ($p=0.028$) to chocolate taste cues. TPD, compared to placebo, increased ventral ($p=0.021$) and dorsal ($p=0.013$) striatum activation to high vs. low reward probability cues, and decreased insula responses ($p=0.018$) to high vs. low aversion probability cues (all p-values are Bonferroni corrected).
Conclusions: At first sight, our results seem to suggest that TD and TPD have opposite effects on reward and aversion processing. However, the increased activation to high vs. low reward probability cues after TPD was driven by decreased responses to low probability cues, suggesting an insensitivity to infrequent rewards. TD was linked to increased anticipatory aversion processing independent of probability. These findings parallel observations of negative biases and reduced reward responsiveness in depression.
Supported By: Medical Research Council (UK)
Keywords: Acute Tryptophan Depletion, Acute Tyrosine/Phenylalanine Depletion, Reward Processing, Dopamine, Serotonin

S74. Perspective of Personalized Drug Treatment in Depression

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Background: Current antidepressants are safe and effective for the majority of patients, but the time until substantial improvement can take weeks or even months. Antidepressants of all classes act mostly unspecific, especially in higher doses, by globally enhancing monoaminergic neurotransmitter activity. This is contrasted by the heterogeneity of depression symptoms suggesting that specific antidepressant treatments personalized to the individual's impairments should be superior to current treatment approaches.
Methods: Personalized treatments require the selection of specific subpopulations of patients characterized by a disease-relevant impairment of the targeted response system. Potential biomarkers identifying such subgroups will be presented, and appropriate treatments for such subgroups will be discussed.
Results: Impaired balance between slow-wave and rapid eye movement (REM)-sleep and disturbed stress response regulation are typical syndromes in acute depression. Converging evidence from animal studies and clinical data suggest an involvement of central corticotropin releasing hormone (CRH) overexpression in imbalanced REM-sleep, while an impaired stress response seems to be majorly driven by an overexpression of certain stress response regulating genes like FKBP5. A re-analysis of a phase-I clinical trial confirms that elevated REM density at baseline predicts response to a CRH-receptor-1 antagonist in major depression, while observational findings from a large longitudinal clinical trial suggest that reduced FKBP5 expression leading to clinical improvement, which, was modulated by genetic variants in the FKBP5 gene.
Conclusions: We conclude that elevated REM-sleep abnormality and FKBP5 genotype might be promising candidates for identifying patients benefiting from CRH-receptor-1 and FKBP51 antagonists, respectively, serving as examples for personalized treatment approaches in major depression.

Supported By: German Federal Ministry of Education and Research (FKZ 01ES0811, 01EE1401D)
Keywords: Major Depression, Biomarkers, CRHR1 Antagonist, FKBP5, Personalized Medicine

S75. Suicide: Out of Time?

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Background: Approximately 50% of suicide attempts are classified as impulsive. Suicide has been hypothesized as a means to immediate relief from overwhelming psychological pain at the expense of future life experiences. Discounting large delayed rewards in exchange for smaller immediate ones is known as cognitive impulsivity. It is unclear whether increases in cognitive impulsivity found in acutely suicidal patients are part of an array of cognitive deficits or due to anomalous time processing. To further examine cognitive impulsivity characteristics in acutely suicidal individuals, we examined associations among time processing, suicidal behavior and cognitive impulsivity. Additionally, we characterized the clinical relevance of impulsivity and time processing by examining relationships with time from suicidal ideation to attempt (TSIA).
Methods: Four groups of adults of both sexes, recent suicide attempters (n=77), suicidal ideators (n=152), non-suicidal depressed controls (n=56), and healthy controls (n=45), were examined for cognitive impulsivity, executive function, and time interval estimation and production. For recent suicide attempters, TSIA was established. ANOVA and linear regression analyses were used.
Results: Impulsive choice, as delayed discounting, was increased in recent attempters and ideators compared to groups of controls (t=4.13; p=.007). TSIA correlated with time interval estimation (r=-.368; p=.018) and production (r=.322; p=.04). Suicidal ideation severity correlated with time estimation (r=.366; p<.001) and production (r=-.249; p=.002).
Conclusions: Increased cognitive impulsivity seen in suicidal patients is associated with both executive dysfunction and slowed time processing. Slower perception of time in suicidal patients may influence a perception of inescapability of psychological pain favoring impulsivity.
Supported By: Clinician Scientist Program of the University Arkansas for Medical Sciences, TRI NCATS UL1TR000039 and by NIGMS P30 GM110702.
Keywords: Suicide, Time Perception, Cognitive Impulsivity, Inpatient

S76. Under Pressure – Is Therapy Refractory Depression a Disorder of CSF-Secretion?

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Background: Increased aldosterone (Aldo) levels and central mineralcorticoid-receptors (MR) activation are linked to therapy resistance to antidepressants. Apart from regulating of slow-wave-sleep, heart-rate-variability, salt preference, aldosterone affect the secretion of cerebrospinal fluid.
Methods: 17 patients with major depression, who were part of a larger study, were examined 3 times during 6 weeks. 13 completed the study. Central and peripheral MR related biomarkers (saliva aldo and cortisol; SWS, HRV, SP) and psychometrics were determined as well as magnetic-resonance-imaging (MRI, 3 tesla) measures of the volume of specific anatomical areas, using Freesurfer 6 software for automatic volume detection.
Results: Response and outcome, as characterized with the HAMD-21 and CGI-S, respectively, is highly negatively correlated with the volume of the lateral ventricles and the total ventricular volume, the size of the choroid plexus (all p<0.05), and by trend with the volume of the central (CCC) and mid anterior corpus callosum (MACC) (p<0.1). The MACC is typically affected my ventricular hypertension These effects were not related to age, but to body mass index (BMI) (p<0.01), a well-known risk factor for ventricular hypertension. Aldo was by trend inversely correlated with CCC and MACC volume (p<0.1). Systolic blood pressure (SBP) was not related to ventricular parameters.
Conclusions: In addition to neuronally mediated MR activated effects of high aldosterone indirect effects via an increase in ventricular volume and mechanical compression of the corpus callosum could be related to therapy refractoriness in depression.
Keywords: Mineralocorticoid Receptor, Cerebrospinal Fluid, Treatment Refractory Depression

S77. Genetic Variants in the ABCB1-Gene Determine Bioavailability of Antidepressants in the Brain

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Background: Antidepressants are the first-line treatment of major depressive disorder, but response rates following the first antidepressant medication are moderate.

Clinical efficacy requires to overcome the blood-brain-barrier where p-gp molecules are located. If they recognize and bind an antidepressant they pump it back into the circulation. If the antidepressant is not recognized the passage is not impaired by p-glycoproteins.
Methods: ABCB1-gene variants were determined with sequencing (Illumina Bead), substrate property analysis employed mice with deletion of ABCB1-analog genes. Clinical protocols followed those of the MARS-project.
Results: 1. The SNPs rs2032583 and rs2235015 provide the best clinical information about blood-brain-penetrance, with CC/CT and TT/GT being the favourable gene variants whereas TT and GG are less favourable. This distinction holds only true if antidepressants are p-glycoprotein substrates.

2. In the presence of the favourable gene-variant patients treated with an antidepressant that is a p-glycoprotein substrate are more likely to remit in shorter time.
3. In the presence of the less favourable gene-variant treatment with a substrate, higher dosages and augmentation strategies, or switch to non-substrates are recommended.
Conclusions: From these data a treatment algorithm was developed that maximizes treatment benefit and minimizes adverse effects.
Supported By: HMNC Holding GmbH, Munich
Keywords: ABCB1 Gene Test, Pharmacogenetics, Antidepressants, Blood Brain Barrier, Bioavailability

S78. Developing a Standardized Taxonomy of Circuit Dysfunction Related to Phenotypes of Mood and Anxiety Disorder

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Background: Large-scale circuit dysfunctions reflecting intrinsic brain organization — default mode, salience and attention — and evoked by specific tasks - negative affect, positive affect and cognitive control - are implicated in mood and anxiety disorders. However, it remains unclear if specific circuit dysfunctions induce specific behavioral phenotypes.
Methods: 160 unmedicated participants with MDD, GAD and specific anxiety disorders underwent functional imaging. Assessments involved facial emotion viewing (negative and positive affect circuits), Go-NoGo (cognitive control circuit), and task-free conditions (intrinsic circuits). Circuit nodes were defined by a synthesis of the current literature, and operationalized using a step-wise procedure. A "circuit dysfunction fit" score for each individual was computed, summarizing the extent of activation and connectivity dysfunction within each circuit. Clinical phenotypes were assessed using self-report scales and a computerized battery of cognitive and emotional tests.
Results: We tested whether within-circuit dysfunctions map to specific behavioral phenotypes, and which combinations of circuit dysfunctions predict these phenotypes. Regression results suggest distinct relations with phenotypes for intrinsic and task-evoked circuit dysfunctions. Salience circuit is central in the manifestation of anxious arousal, threat-related stress and anhedonia. Attention circuit dysfunction contributes to negative ruminative attributions, anhedonia and poor attention. In task-evoked conditions, negative affect circuit dysfunction contributed to anxious avoidance and associated behavioral performance. Negative affect circuit dysfunction also contributed to poor attention.
Conclusions: We present a standardized definition and set of metrics for operationalizing circuit dysfunctions that cut across diagnoses of psychiatric disorders with the aim to advance a clinically relevant brain circuit-based taxonomy.
Supported By: R01
Keywords: Functional Neuroimaging, Phenotype, Mood Disorders, Anxiety Disorders

S79. Dual Task Cost: A Functionally Relevant Measure of Psychomotor Retardation and Depressive Rumination in Patients With Major Depressive Disorder

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Background: Recent studies have demonstrated that the assessment of postural performance may be a potentially reliable and objective marker of the psychomotor retardation (PMR). We aimed at investigating the interplay between the severity of depression, cognitive slowing due to compelling depressive rumination and the centre of pressure (CoP) velocity based postural assessment under dual-tasking condition.
Methods: Compared with 24 age- and body mass index-matched healthy controls (HC), 26 patients with MDD performed postural assessment of the CoP dynamical scores under three experimental tasks: (1) single referent task (a quiet stance), (2) actual posture-motor dual-task (AMT); (3) mental (i.e., imaginary) version of the same task (MMT). All the tasks were performed in the eyes open (EO) and the eyes closed (EC) conditions.
Results: In the EO condition the CoP assessment scores were similar in HC and patients under single and dual-tasking paradigms. The EC condition induced overall increase of postural instability in HC and patients. Meanwhile, for this condition, patients vs. HC manifested larger postural deficit in the single task, which was reliably and significantly attenuated by MMT and AMT dual-tasking activity. A multiple linear regression analysis evidenced that CoP assessment reactivity scores under the dual-tasking in the EC condition significantly predicted clinical scores of both depression and depressive rumination.
Conclusions: The findings allow us to suggest that execution of concurrent timed fine motor (actual or even imaginary) task with closed visual input deallocates attentional resource from compelling depressive rumination (such as, e.g., brooding) thereby attenuating the depression-related PMR.
Supported By: Research was supported by Russian Science Foundation grant #16-15-00128 to Lyubomir Aftanas
Keywords: Major Depressive Disorder (MDD), Psychomotor Retardation, Depressive Rumination, Posture-motor Dual Tasking, Posture-Ideomotor Dual Tasking

S80. Individual Differences of Spontaneous Angular Gyrus Brain Activity in Dissociating Moral Injury and Posttraumatic Stress Disorder

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Background: Moral injury refers to guilt- and shame-based disturbances often experienced by combat veterans who have violated their own deeply held moral and ethical beliefs and expectations. It is associated with, but conceptually and mechanistically different from posttraumatic stress disorder (PTSD), which implicates threat/fear neurocircuits. Moral injury events are explained by two factors: perceived transgression and betrayals. Unfortunately, little is known about the neural differences between moral injury and PTSD, and the neural correlates of the two factors of moral injury.
Methods: Multiple regression model was employed in 26 participants (2 females; 28∼55 yrs) to investigate the relationship between the amplitude of low frequency fluctuation (ALFF) of resting-state functional magnetic resonance images and scores on: 1) Moral Injury Events Scale (MIES), and 2) Clinician Administered PTSD Scale (CAPS).
Results: Larger ALFF in the left angular gyrus is associated with higher scores of perceived transgressions ($R=0.699$, $p<0.001$) and lower scores of perceived betrayals ($R=-0.763$, $p<0.001$) on the MIES. No relationship was found between ALFF and PTSD symptoms ($R=-0.080$, $p=0.746$). The three correlations were significantly different between each other ($ps<0.005$).
Conclusions: This is the first evidence that moral injury and PTSD have distinct and dissociable neural correlates. Furthermore, the left angular gyrus, which is strongly implicated in social cognition and moral decision making, plays different roles in transgression and betrayal components of moral injury. The findings increase our knowledge of PTSD and moral injury as distinct entities, which may contribute to developing new diagnoses and interventions for individuals struggling with moral injury.
Supported By: The Department of Veterans Affairs' (VA) Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC) of the VA Office of Mental Health Services; the Mid-Atlantic Healthcare Network
Keywords: Moral Injury, Resting-State fMRI, Angular Gyrus

S81. Unique Pharmacology and Clinical Evidence Supporting the Antidepressant Therapeutic Potential of Lumateperone

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Background: Lumateperone (ITI-007) is a first-in-class investigational agent which simultaneously modulates serotonin, dopamine, and glutamate neurotransmission, currently in clinical development for schizophrenia, bipolar depression and agitation associated with dementia
Methods: We report on the unique pharmacology of lumateperone, highlighting mechanisms which are supportive of antidepressant effects. We detail existing clinical data supporting antidepressant efficacy. Lumateperone has been evaluated for efficacy and safety in three late-stage trials in patients with acute schizophrenia and for safety in an open-label switching study in patients with stable schizophrenia; subgroup analyses were conducted in patients with comorbid depression. Lumateperone is being evaluated in three late-stage placebo-controlled trials in patients with bipolar depression
Results: Lumateperone is a potent antagonist at 5-HT2A receptors and exhibits serotonin reuptake inhibition. Lumateperone also binds to dopamine D1 and D2 receptors acting as a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with pre-synaptic partial agonism and post-synaptic antagonism at D2 receptors and as an indirect glutamatergic (GluN2B) phosphoprotein modulator with D1-dependent enhancement of both NMDA and AMPA currents via the mTOR protein pathway. Improvement in symptoms of schizophrenia was demonstrated for ITI-007 60mg. Comorbidly depressed patients experienced meaningful improvements in depressive symptoms. Lumateperone had a placebo-like safety profile and was not associated with the adverse events (e.g. weight gain, cardio-metabolic disturbances and movement disorders) typically seen with antipsychotic medications.
Conclusions: The pharmacology of lumateperone suggests broad and rapid control of antidepressant symptoms. Lumateperone represents a potential new approach for the treatment of a range of mood disorders.
Keywords: Rapid Antidepressant, mTOR, Glutamate Receptors, Dopamine D1 Receptors, Dopamine D2 Receptors

S82. Evidence of a Shift in the Excitability of the Glutamatergic Neurotransmission in the Anterior Cingulate During Appraisal of Emotional Stimuli That is Influenced by Aerobic Fitness

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Background: Neuroticism and fitness influence appraisal of emotional stimuli and coping strategies ultimately impacting health. Exercise improves stress regulation as well as cognitive and emotional processing. Here we examine the relationship between fitness and personality on the neurobiology of emotion using task-based ^{1}H MRS.
Methods: Personality and fitness were measured in twenty healthy individuals using the NEO Personality Inventory and maximal oxygen consumption (VO2max), respectively. During a separate visit, 1H fMRS (PRESS; TE=23ms; TR=2.67s; 8avg/measurements; 6 measurements/block; 3 blocks) was used to investigate the response of the neurotransmitters glutamate in the dACC (3.4cm3 volume) during an image appraisal task using the Nencki Affective Picture System. The ^{1}H fMRS paradigm included randomized blocks of primarily positive (E+), Negative (E-), or neutral (En) images. Response of glutamate to stimulus type was assessed using a Mixed Model with repeated measures within subject.
Results: Glutamate levels in the dACC were significantly lower during appraisal of E+ compared to En ($F = 4.46$, $p=0.012$).

VO2max exhibited a negative association with dACC glutamate modulation in response to E- (r=-0.474, p=0.039).
Conclusions: These results show dynamic changes in the ACC glutamatergic neurotransmission across the appraisal of pictures. The lower glutamate levels during the appraisal of positive emotional valence compared to neutral pictures reflects a shift in the excitatory/inhibitory balance towards decreased excitability. Greater aerobic fitness was associated with a higher delta change in glutamate relative to En during appraisal of negative images. These results expand our understanding of personality and fitness on brain function.
Supported By: This work was supported by NIDDK grant DK092322, and BBRF NARSAD Young Investigator Award to PRB
Keywords: Emotion Appraisal, Cardiopulmonary Exercise Testing, Personality

S83. 5-HT1A, 5-HT2A, and SERT Binding in Auditory Cortex in Major Depressive Disorder

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Background: The superior temporal gyrus (STG) receives some of the highest density serotonergic innervation in the telencephalon. Serotonin (5-HT) modulates the response magnitude in primary auditory cortex (A1) to different sound intensities, with more 5-HT decreasing response magnitude. This auditory response has predicts response to SSRIs in major depressive disorder (MDD). We sought to determine serotonin transporter (SERT), 5-HT1A and 5-HT2A receptor binding in A1 and secondary auditory cortex (A2) in MDD and controls.
Methods: Post-mortem brain samples from 141 healthy controls (HC) and 41 subjects with MDD were studied. 5-HT1A receptor (3H-DPAT), 5-HT2A binding (3H-ketanserin) and SERT binding (3H-cyanoimipramine) was quantified in A1 (BA41, HC n= 14, MDD n=10) and A2 (BA 21 and 22, HC n= 115, MDD n= 37).
Results: MDD demonstrated 24% lower 5-HT2A binding in A1 compared to controls (MDD mean 22.8 fmol/mg tissue, std 7.6; HC mean 30.1 fmol/mg tissue, std 8.1; t-test $p<0.05$). This difference was absent in dorsolateral prefrontal cortex (BA9) and primary motor cortex (BA4). SERT binding was 23% less in MDD than controls in BA22 (MDD mean 5.9 fmol/mg tissue, std 3.9; HC mean 7.7 fmol/mg tissue, std 4.2; t-test $p < 0.05$). 5-HT1A binding was not different between MDD and controls.
Conclusions: MDD is associated with less 5-HT2A receptor binding in A1 and less SERT in A2. These differences may be adaptive changes due to lower serotonergic tone in MDD and may relate to neurophysiological changes observed in auditory cortex in MDD.
Supported By: NIH grant #s MH40210, MH090964, MH46745, MH62185
Keywords: Serotonin, Depression, Serotonin 2A Receptor, Post-Mortem Brain, Auditory Cortex

S84. Interplay Between Fronto-Limbic Resting State Connectivity and Hypothalamic-Pituitary-Adrenal Axis Functioning in Adolescents With and Without Self Injury

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Background: Major Depressive Disorder (MDD) is associated with abnormal stress system functioning, which includes dysfunction within the hypothalamic-pituitary-adrenal (HPA) axis and in resting-state functional connectivity (RSFC). Further, non-suicidal self-injury (NSSI) is fairly common among adolescents with MDD and is associated with a unique pattern of stress system functioning. However, RSFC and its relationship with cortisol response has not been examined among adolescents with MDD and NSSI.
Methods: We examined associations between cortisol and amygdala-medial prefrontal cortex (mPFC) RSFC in 83 adolescents aged 12-19 years with MDD and with NSSI (MDD/NSSI; n=29), MDD without NSSI (MDD; n=21), and controls (HC; n=33). Measures include mean z-scores extracted from the mPFC from individual amygdala RSFC maps and area under the curve (AUC) and deviation from linearity scores for cortisol levels during the Trier Social Stress Test (TSST) and upon awakening (CAR).
Results: Right amygdala-mPFC RSFC and group interaction significantly predicted TSST AUCg, F=2.37, p=.04 (MDD: r=-.26, p<.01; MDD/NSSI: r=-.16, p=.07; HC: r=.01, p=.18). Mean amygdala-mPFC RSFC and group interaction marginally predicted CAR deviation, p=.10, and was significant for females, F=3.75, p=.01 (MDD: r=-.25, p=.07; HC: r=.48, p=.001. MDD/NSSI: r=-.02, p>.45). In MDD/NSSI, CAR and TSST AUCg are positively related, r=.64, p=.001.
Conclusions: Neural and HPA stress systems show coordination in MDD but fronto-limbic hyperconnectivity may interfere with HPA system recruitment efficiency. MDD/NSSI show blunted HPA responding and a lack of coordination across stress systems. This study underscores the importance of multiple levels of analysis approaches to understanding stress system functioning.
Supported By: Deborah E. Powell Center for Women's Health Seed Grant, National Institute of Mental Health (K23MH090421), National Alliance for Research on Schizophrenia and Depression, the University of Minnesota Graduate School, Center for Neurobehavioral Development, and the Minnesota Medical Foundation
Keywords: Resting State Functional Connectivity, HPA Function, Adolescent Depression, Fronto-Limbic Connectivity, Non-Suicidal Self-Injury

S85. Dynamic Factor Structure of the Hamilton Depression Rating Scale During Electroconvulsive Therapy in Major Depression

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Background: The Hamilton Depression Rating Scale (HDRS) remains the gold standard for the assessment of depression severity. Several prior studies have addressed the factor structure of the HDRS in depression. However, none have evaluated dynamic changes in HDRS factor structure in the context of electroconvulsive therapy (ECT).
Methods: 157 ECT patients (age=49.5+/-4.3 years; 96 females) from 4 independent sites participating in the Global ECT-MRI Research Collaboration, all experiencing a DSM-IV defined major depressive episode, were recruited. Depression severity was assessed with the HDRS-17 before and after treatment. Oblimin rotations were used to factor HDRS items at baseline, follow-up, and item-level changes (follow-up − baseline scores) over ECT. Bayesian estimation determined the credibility of HDRS item-level changes.
Results: Five items were reliably reduced over ECT treatment: depressed mood, guilt, suicide, work, and psychic anxiety. Item-level change separated into two factors separating insomnia from other items, though suicide, weight loss, genital, and insight items did not load well on either factor. Baseline HDRS items loaded onto three factors generally segregating core, somatic, and insomnia symptoms; guilt, agitation, somatic symptoms, genital, and insight items did not adequately load on any factors. A two-factor solution separated insomnia from all other items at follow-up; however, insight did not load on any item above 0.4.
Conclusions: ECT differentially affects symptom dimensions of depression. HDRS items reflective of the core aspects of depression are most improved with ECT. Item-level covariance structures differ between baseline and follow-up with certain items systematically lacking coherence with prominent dimensions of depression symptomatology.
Supported By: R01MH092301; K24MH102743
Keywords: Major Depression, Electroconvulsive Therapy (ECT), Factor Analysis, Bayesian Model

S86. Vesicular Monoamine Transporter (VMAT2) Binding in Platelets as a Biomarker for Severity of Major Depressive Disorder

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Background: Monoamine neurotransmission has been implicated in major depressive disorder (MDD). Vesicular monoamine transporter-2 (VMAT2) sequesters cytosolic monoamines inside presynaptic vesicles in neurons, as well as in platelets, which can be used as an accessible peripheral model.
Methods: Platelet VMAT2 maximal binding sites (Bmax) and equilibrium dissociation constant (Kd) were measured using [3H]dihydrotetrabenazine ([3H]TBZOH) as a ligand in adult MDD patients (n=22) without current substance use disorders. Patients were recruited in high and low suicide risk groups, age- and sex-matched. High risk was defined as suicide attempt within 5 years or current suicidal ideation with intent and/or plan; low-risk patients had no lifetime suicide attempts and no current suicidal ideation. Depression severity, suicidal ideation, hopelessness, and lifetime aggression were evaluated. VMAT2 binding kinetics were compared between high- and low-risk groups and were correlated with clinical symptoms.
Results: No differences were seen in VMAT2 binding kinetics between low- and high-suicide risk groups, or in suicide attempters compared with non-attempters. Depression severity, measured by the Hamilton Depression Rating Scale, inversely correlated with VMAT2 Bmax ($r=0.55$, $p=0.008$) and Kd ($r=0.57$, $p=0.006$). Results did not change after removing 3 low-risk and 4 high-risk patients on psychiatric medications; or removing 3 patients with past alcohol use disorder and 2 patients with past cannabis use disorder. No other clinical measure, including suicidal ideation, correlated with VMAT2 binding kinetics.
Conclusions: Lower VMAT2 Bmax may indicate deficient presynaptic monoamine uptake in vesicles as a pathogenetic mechanism in MDD related to severity of depression, but not directly related to suicide risk.
Supported By: American Foundation for Suicide Prevention (AFSP; PI: Sublette), T32-MH15144 (PI: Fitzgerald), NIMH Conte Center P50MH090964 (PI: Mann)
Keywords: Major Depressive Disorder (MDD), Suicide, Mood Disorders, Platelets, VMAT2

S87. Toward Emotion Prosthetics: Emotion Regulation Through Wearable Vibroacoustic Stimulation

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Background: Chronic stress is prevalent, expensive, and has a negative effect on people's lives. Current technologies for changing reactions to stress generally involve therapies that can take months yielding techniques that may not be accessible by individuals in the moment, and medications that have undesirable side effects, all of which are associated with

response in only about half of those who receive them. Thus, there is a priority on developing novel, often technology-based approaches that are easy and inexpensive to implement, and ideally, that target implicated mechanisms directly to apply the ideals of personalized medicine.
Methods: Here, we consider the impact of externally administered chest and wrist tactile vibration on subjective, behavioral, and psychophysiological reactivity to a laboratory stressor. Thirty-eight participants completed a laboratory stressor task under randomized conditions of no vibration or multiple frequencies of wrist or sternal vibratory stimulation.
Results: Data suggested that a majority of individuals were affected by vibratory stimulation with some individuals experiencing profound reductions in subjective and physiological indicators of stress along with increases in behavioral performance. Our findings provide some of the first evidence that tactile vibratory stimuli can reliably alter subjective experience, parasympathetic activity, and performance on stressful cognitive tasks in tandem.
Conclusions: These findings suggest that vibratory stimuli can predictably modulate the processing of the conscious experience in the moment as a novel therapeutic tool for treatment of medical and psychiatric conditions thought to be related to dysregulation of the ANS including, but not limited to, PTSD, anxiety, asthma, agitation, fibromyalgia, chronic pain, and IBS.
Supported By: University of Pittsburgh
Keywords: Neuromodulation, Affective Disorders, Vibroacoustic, Parasympathetic-Sympathetic Balance

S88. Young Male 'Owls' Present With Decreased Levels of Brain-Derived Neurotrophic Factor: Increased Risk for Depression?

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Background: Brain-derived neurotrophic factor (BDNF) is involved in neuroplasticity, and decreased BDNF activity is related to pathophysiology of depression. Moreover, BDNF follows a circadian rhythm with a peak early after awakening and a gradually decline thereafter. The aim of this study was to examine, if BDNF serum levels (BDNF i. s.) in the afternoon would depend on the chronotype. We expected a phase advance in healthy 'owls' with higher BDNF serum levels in the afternoon than in 'larks'.
Methods: In 47 healthy men (age: 22.3 ± 3.2 y) the chronotype was determined with the Morningness-Eveningness-Questionnaire (MEQ), with high scores indicating a morning type ('lark') and low scores representing an evening type ('owl'). Blood samples for analysis of BDNF i. s. were collected at 2 p.m. and total BDNF i. s. was determined by ELISA.
Results: 19.1% of the sample represented an evening type, 10.6% a morning type and 70.2% an indifferent type. BDNF i. s. correlated positively with the MEQ score ($r = 0.30$, $p = 0.04$). 'Larks' had higher BDNF i. s. levels than 'owls'" (36.8 ± 6.3 ng/ml vs. 24.8 ± 10.4; $p = 0.038$) at 2 p.m.
Conclusions: 19.1% of the sample represented an evening type, 10.6% a morning type and 70.2% an indifferent type. BDNF i. s. correlated positively with the MEQ score ($r = 0.30$, $p = 0.04$). 'Larks' had higher BDNF i. s. levels than 'owls'" (36.8 ± 6.3 ng/ml vs. 24.8 ± 10.4; $p = 0.038$) at 2 p.m.
Keywords: BDNF, Sleep, Chronobiology

S89. Dimensions of Anhedonia Associate With Dissociable Neurostructural Measures Across Psychiatric Disorders

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Background: Anhedonia is multi-faceted and impacts multiple psychiatric disorders. Prior studies have implicated altered cortico-striatal abnormalities in the pathophysiology of anhedonia. However, it is unknown to what extent structural abnormalities in these circuits are shared across diverse psychiatric disorders. Furthermore, it is unknown how structural deficits contribute to distinct aspects of anhedonia.
Methods: The patient sample (total n=304) included schizophrenia (n=83), bipolar disorder (n=61), major depressive disorder (n=35), psychosis risk (n=39), and healthy controls (n=86). All participants completed both detailed anhedonia phenotyping and structural imaging at 3T. A bi-factor analysis was used to identify both overall and specific dimensions of anhedonia. Structural image processing used ANTs to create a custom T1 template and estimate cortical thickness (CT). Both CT and gray matter volume (GMV) were summarized within anatomically-defined regions using an advanced multi-atlas labeling procedure. Analyses related anhedonia factors to structural brain measures; the False Discovery Rate was used to correct for multiple comparisons ($Q<0.05$).
Results: The bi-factor model identified factors related to overall general anhedonia, social anhedonia, physical anhedonia, behavioral activation and anxious misery. General anhedonia was associated with decreased GMV in right middle temporal gyrus, temporal pole, entorhinal area and left superior parietal lobule. Social anhedonia was associated with decreased CT in the left inferior frontal gyrus, left lateral orbital gyrus, and right inferior frontal gyrus.
Conclusions: These results demonstrate dissociable relationships between sub-domains of anhedonia and neurostructural measures across psychiatric disorders. Disruption of these reward-related brain regions could underlie distinct transdiagnostic dimensions of anhedonia, and point to new therapeutic targets.
Supported By: National Institutes of Mental Health (R01, K23)
Keywords: Neuroimaging, Structural MRI, NIMH Research Domain Criteria, Mood Disorders, Psychotic Disorders

S90. Social Defeat Stress: A Plasma Proteomic Study to Identify Stress Susceptible-Associated and Resilience-Associated Biomarkers

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Background: It has been widely described that chronic stress is a strong risk factor for mental health in individuals that are genetically or environmentally predisposed. To investigate neurobiological mechanisms and pathways underlying stress-related symptoms of psychiatric disorders we used proteomics methods to investigate changes in a model of social defeat stress.
Methods: Serum was collected from mice that underwent chronic social defeat stress and were identified as control, susceptible, or resilient (n=5 per group). The blood was collected, allowed to clot at room temperature and then spun at 4°C. Plasma was depleted of the three most abundant proteins, i.e. albumin, IgG, and transferrin. Unbiased shotgun proteomics incorporating label-free quantitation was used to identify differentially expressed proteins.
Results: 170 proteins passed the initial quality check, i.e. proteins were identified in at least 80% of samples. Repeated measures analysis within the susceptible group comparing day 0 and 30 revealed 55 proteins to be significantly differentially expressed ($p<0.05$), of which 20 were FDR positive. Repeated measures analysis within the Resilient group comparing day 0 and 30 revealed 30 proteins to be significantly differentially expressed, of which 19 were FDR positive. Pathway analysis (KEGG, David NIH) of the significant proteins determined "complement and coagulation cascades" to be the top pathway with 6 complement proteins in the susceptible group being significant (Cfi, C9, C8g, C5, C4bpa and C2) and 9 proteins significant in the resilient group (Cfh, Cfi, C9, C8g, C1qb, C1ra, C5, C4b and C1qc).
Conclusions: We found that proteins involved in the Complement and Coagulation system are dysregulated and further work is currently under way to validate these findings in a human stress model.
Keywords: Proteomics, Stress Exposure, Complement Proteins

S91. Omega-3 Polyunsaturated Fatty Acid Enrichment Increases Prefrontal Activation in Response to Repeated Ketamine Administration

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Background: Mood and psychotic disorders are associated with deficits in long-chain omega-3 (LCn-3) fatty acids including docosahexaenoic acid (DHA). We previously reported that prefrontal cortex (PFC) glutamate levels are inversely correlated with DHA levels in rats fed diets with varying n-3 levels. To further investigate the role of LCn-3s on glutamate homeostasis, this study evaluated the effects of ketamine, a glutamate NMDA receptor antagonist, on behavior and neuronal signaling.
Methods: From P21-P90, male rats were fed a diet with preformed DHA (fish oil, FO), no n-3 fatty acids (Deficient, DEF), or a control diet (CON). From P86 to P90, rats received ketamine injections escalated daily (5, 10, 20, 30 mg/kg), and locomotor activity collected post-injection. Rats were sacrificed 90 minutes after the final injection and the PFC was isolated for qRT-PCR analysis.
Results: After 10 mg/kg ketamine there was a significant effect of diet, with DEF rats exhibiting greater activity. At the 30 mg/kg dose, there was a significant diet by time interaction, and locomotor activity was initially reduced in DEF and CON rats, but not FO rats. Following 30 mg/kg ketamine, expression of c-Fos, a marker neuronal activation, was significantly greater in the PFC of FO rats. mGluR1 and Glut3 expression were also significantly elevated in the PFC of FO rats.
Conclusions: These findings suggest that LCn-3 enrichment enhances neuronal activation in the PFC in response to repeated ketamine administration. These findings may have implications for understanding the role of DHA biostatus in the psychotropic effects of ketamine.
Supported By: This work was supported in part by National Institute of Health grant MH107378 to R.K.M.
Keywords: Ketamine, Prefrontal Cortex, Locomotor Activity

S92. Ankyrin-G Heterozygous Knockout Mice Display Increased Sensitivity to Social Defeat Stress

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Background: The Ank3 locus, coding for Ankyrin-G (Ank-G), confers an increased risk for bipolar disorder in GWAS. Mice with conditional homozygous knockout (cKO) of Ank-G in the adult forebrain (Zhu et al. PNAS 114:10479-10484, 2017) have hyperactivity and reduced "anxiety" reminiscent of human mania at baseline, and "depression-like" behaviors when exposed to social defeat stress (SD). Ankyrin-G heterozygous knockouts (Hets) have not yet been characterized.
Methods: Behaviors of adult Hets and control littermates were assessed via open field activity, forced swim test, and elevated plus maze (EPM). Mice were then exposed to 4-, 10-, or 14-days of SD after which they were again behaviorally tested. In a separate cohort, Hets and controls were exposed to 4-day SD or standard conditions followed by behavioral testing. In a third cohort, Hets and controls were exposed to 14-day SD followed by 14-day treatment with fluoxetine or vehicle, and post-treatment behavioral testing.
Results: At baseline, Ank-G Hets were similar to controls. After 4- and 10-day SD, Hets spent less time in the EPM open arm compared to stressed controls. In a separate cohort, only

Hets displayed depression-like behavior after 4-day SD. After 14-day SD, Hets and controls displayed similar stress-induced phenotypes, which were reversed by fluoxetine treatment.
Conclusions: Ank-G Hets are similar to controls at baseline, but display increased sensitivity to SD compared to controls. The stress-induced phenotype responds to fluoxetine. These Ank-G genetic models may provide insights into the role of Ank-G in the pathophysiology of stress sensitivity and potentially into neurobiology related to bipolar disorder.
Keywords: Transgentic Animal Model, Bipolar Disorder, Ankyrin-G, Chronic Social Defeat Stress, Behavior

S93. Concurrent Antidepressant Use is Not Associated with Different rTMS Treatment Outcomes for Major Depressive Disorder in a Sham-Controlled Trial

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Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment for patients with major depressive disorder (MDD) who do not respond to, or are unable to tolerate pharmacological treatments. The large regulatory controlled clinical trials establishing TMS efficacy prohibited concurrent use of psychotropic medications. Few studies have examined the effect of concurrent medication on rTMS outcomes.
Methods: A randomized, double-blind, sham-controlled trial examined the efficacy of 2-coil TMS in MDD subjects who were allowed to continue stable doses of their prior medications (n=92) (Carpenter et al 2017). 20 daily rTMS treatment were delivered at 10 Hz (maximum summated power for both coils <=120% of motor threshold) with coil centers positioned over left dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC).
Results: In the intention-to-treat (ITT) sample (n=92), concurrent antidepressant use (all pharmacological classes combined) was not a significant predictor of response (p=0.6) or remission(p=0.6); results were similar for the per-protocol sample (n=75). Among those who received active stimulation (n=47), no category of concurrent medication except opioid analgesic use was a significant predictor. Concurrent opioid use during rTMS predicted inferior outcome at trend level (p<0.10).
Conclusions: rTMS treatment outcome was not contingent on, or accounted for, by concurrent antidepressant use in this controlled trial, refuting the notion of synergistic effect from medication plus stimulation.
Supported By: Cervel Neurotech, Inc., which was eventually acquired by Rio Grande Neurosciences, Inc.
Keywords: MDD, rTMS, Antidepressant, Treatment Response

S94. Personality Factors in the Selection of Participants for Deep Brain Stimulation for Treatment Resistant Depression

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Background: Treatment resistant depression is a heterogeneous condition, defined primarily by number of treatment failures. Deep brain stimulation (DBS) is a promising experimental treatment for TRD, however there is limited data characterizing those patients who are selected for or responsive to DBS treatment. The NEO-PI-R models personality according to five domains: Neuroticism, Extraversion, Openness, Conscientiousness, and Agreeableness.
Methods: We used the NEO-PI-R to assess personality characteristics of 43 patients who presented for inclusion in a DBS for TRD study, 29 of whom underwent DBS treatment. All had undergone extensive screening and appeared to meet inclusion criteria for the DBS study, including being in a major depressive episode at the time of assessment. T-scores for the 5 factors were compared between those who were and were not ultimately enrolled in the study.
Results: All patients assessed demonstrated high agreeableness, high neuroticism, and very low extraversion. Patients who enrolled in the DBS study scored significantly lower on agreeableness relative to those who were excluded, p=0.02.
Conclusions: This early, exploratory analysis of personality markers for patient selection for DBS for TRD suggests that overly high agreeableness is negatively associated with selection for study inclusion. Higher agreeableness, combined with the other traits observed here, is associated with very inhibited expression of anger and a self-effacing interaction style. This suggests that an overly-accommodating personality type is less likely to be enrolled in an invasive investigational study. Future work will attempt to discern characteristics that differentiate DBS treatment responders from non-responders.
Supported By: Dana Foundation; Hope for Depression Research Foundation; Stanley Medical Research
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Personality

S95. Loudness Dependency of Auditory Evoked Potentials (LDAEP) as a Differential Predictor of Antidepressant Treatment Response in Major Depressive Disorder (MDD): Results From the Sertraline/Placebo-Controlled EMBARC Study

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Background: Loudness-dependent auditory evoked potentials (LDAEP), a monotonic increase of N1/P2 amplitude with increasing tone intensity, has promise as a predictor of clinical treatment response with serotonin agonists in MDD. LDAEP was therefore included in a comprehensive array of putative clinical and biological moderators of treatment effect (rate of change in depressive symptoms across randomized SSRI or placebo treatment [Tx]) in the multisite project Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC).
Methods: MDD patients (baseline HAMD17≥5, 78 sertraline, 86 placebo) who completed Stage 1 (8-wk) provided baseline 72-channel ERPs to 1000-Hz tones at five intensities (60-100 dB). N1 activity attributable to primary auditory cortex (tangential dipole) was quantified using scalp current source density and temporal PCA. Multilevel analysis examined the association of N1 dipole amplitude, Tx, intensity, and rate of symptom change (slope of HAMD scores).
Results: A significant Tx*intensity*symptom change interaction (p=.006) originated from an increasingly stronger association between larger N1 and better clinical response with increasing tone intensity for sertraline only, whereas this association was lower for placebo and did not vary with intensity. At the same time, a significant intensity*symptom change interaction (p=.003) confirmed that a steeper LDAEP N1 slope was linked to symptom improvement, independent of Tx. These effects remained after adding gender, age, and baseline HAMD as covariates to the regression model.
Conclusions: Results confirm and extend prior findings, suggesting that LDAEP as a neurobiological marker may function both as a predictor of MDD treatment response and as a moderator of treatment effect.
Supported By: NIMH; NIH
Keywords: Antidepressant Response, Predictive Biomarkers, ERPs, N100, Sertraline

S96. Wrist Actigraphy in Depressed Suicide Ideators and Non-Ideators Before and After Ketamine

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Background: Annually, almost a million individuals die from suicide. Research suggests sleep disturbances, specifically wakefulness as defined by sleep EEG, are associated with suicidal ideation (SI), supporting the necessity of research designed to delineate sleep-related risk factors for suicide. This investigation examined differences in wrist-actigraphy between patients with and without SI.
Methods: 51 treatment-resistant depressed patients (MDD=34, BP=17, F=29, M=22, age=42.6) underwent 24-hour wrist-actigraphy collection 3-4 days before and 5 days after a single-dose infusion of ketamine(0.5mg/kg). Activity levels were analyzed for two 24-hour periods, each divided into four, 6-hour time bins, before and after ketamine administration. MDD patients were medication-free two weeks before study; BP patients were maintained on mood stabilizers. Patients were divided by reports of SI at baseline, using the suicide item from the Hamilton Depression Rating Scale. Statistical analysis of the relationship of SI to activity was conducted using a linear mixed model.
Results: A main effect of ideation on activity levels at baseline was found(p=.018), such that ideators exhibited lower levels of total 24-hour activity. In patients with SI(n=30), there also was a significant response by time of day interaction between SI responders and non-responders to ketamine(p=.045). Responders exhibited more activity throughout the day post-ketamine, between 6am-5:59pm.
Conclusions: Our findings suggest that suicidal ideators display decreased activity pre-ketamine, and that an anti-suicidal response to ketamine is associated with increased activity. Increased activity may point to biological underpinnings of ketamine's effects on SI. The relationship of these results to previous sleep EEG findings, and changes in depression and energy, will be discussed.
Supported By: National Institute of Mental Health
Keywords: Major Depressive Disorder (MDD), Actigraphy, Suicidal Ideation, Ketamine, Bipolar Disorder

S97. Insomnia is Associated With Response to Ketamine Administration in Patients With Major Depressive Disorder

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[1]National Institute of Mental Health

Background: Dysregulation of sleep is a common feature in depression, including high comorbidity with insomnia. Here we examine how self-rated insomnia relates to the rapid mood improvement effects of ketamine in MDD, and sleep architecture that may contribute to this interaction.
Methods: Participants (n=39; f=21; mean=39.59y) with MDD received a single infusion of ketamine (0.5 mg/kg over 40 minutes). MADRS was ≥22 for inclusion. Participants underwent polysomnography the nights before(BL) and following(K) ketamine infusion to assess REM Time, REM latency, Slow-wave Sleep, Wake After Sleep Onset, Sleep Efficiency, and Total Sleep Time. MADRS scores were taken 60 minutes (60') before ketamine infusion, 230' after, and the following day (1440'). Insomnia was self-reported at -60' using items 6-8 from the HAM-D (Early/Middle/Late Insomnia, or EI/MI/LI). Associations between sleep measures were associated using Pearson's correlation.
Results: Elevated BL EI scores correlated with poor post-ketamine mood response from -60' to 230' (r=.378, p=.009). At BL, elevated LI, but not EI, was associated with higher pre-infusion MADRS score at -60' (r=0.476, p=0.001), but did not associate with mood change at 230'.

Short BL REM latency correlated with poor mood response from -60' to 230' (r=-.301, p=.033). At BL, short REM latency was correlated with elevated EI (r=-.330, p=.022), MI (r=0.338, p=.019), and LI (r=-0.323, p=.024).
Conclusions: Elevated EI at BL was linked to a diminished acute response to ketamine. The fact that EI scores were also

correlated with REM latency suggests that REM sleep architecture may be an important consideration for developing individualized treatment to ketamine.
Supported By: NIMH
Keywords: Major Depression, Insomnia, Ketamine, REM Sleep, Treatment Response

S98. Effect of GLP-1 Agonists Use on Cognitive and Affective Functioning in Type 2 Diabetes Mellitus Patients: A Preliminary Study

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Background: Glucagon-like peptide-1 (GLP-1) agonists are used in the treatment of type 2 diabetes (T2DM). However, GLP-1 receptors are also proposed to play a role in mood and cognition given their widespread expression in the brain. Here, we aimed to study the effects of GLP-1 agonists (GLP-1A) on cognitive and affective functioning by assessing T2DM patients with or without GLP-1A treatment.
Methods: 31 T2DM patients (17 on GLP-1A, 14 without GLP-1A) were evaluated with: Snaith-Hamilton Pleasure Scale, Cognitive Failures Scale (CFS), PHQ9, GAD7, childhood trauma questionnaire (CTQ) and chronic stress (CS). They performed laboratory-based measures of reward learning (the probabilistic reward task; PRT) and working memory (letter-n-back task; LNB).
Results: Patients on GLP-1A reported higher PHQ9 (9.65 ± 5 vs. 6.21 ± 4, $p=0.04$) and CFS (29.3 ± 13 vs. 20.8 ± 11, $p=0.04$) scores. They also had higher false positive results on LNB (2.8 ± 2.5 vs. 0.83 ± 1.3, $p=0.008$), but exhibited no differences in response bias or discriminability as assessed by PRT (both ps$>$.05). Multivariate linear regression analyses entering GLP-1A use, age, gender, education, CS and CTQ revealed that CS was the only predictor of PHQ9 and CFS scores ($p<0.001$ and $p=0.048$, respectively) leading GLP-1A use to be insignificant.
Conclusions: Contrary to our hypothesis, our preliminary analysis shows that patients on GLP-1A reported higher depressive scores and cognitive failures, however this effect was significantly modulated by chronic stress levels.
Keywords: GLP-1 Agonist, Reward Learning, Working Memory, Diabetes Mellitus

S99. Evaluation of Abuse Potential of Samidorphan in Healthy, Nondependent, Recreational Opioid Users

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Background: The abuse potential of samidorphan (SAM), a μ-opioid receptor antagonist derived from naltrexone (NAL), was evaluated versus active comparators in a double-blind, placebo (PBO)-controlled study of healthy, nondependent, recreational opioid users.
Methods: Following a qualification phase, participants were randomized to 1 of 6 treatment sequences that included the following treatments: PBO, SAM (10 or 30mg), oxycodone (OXY; 40mg), pentazocine (PEN; 30mg), and NAL (100mg) in a 6x6 crossover design. The primary endpoint was maximum effect (Emax) for Drug Liking ('at the moment') visual analogue scale (VAS) score. Secondary endpoints included Take Drug Again and Overall Drug Liking VAS scores and safety assessments. Between-group, within-subject differences in VAS scores were compared.
Results: Forty-seven participants comprised the evaluable population. Emax Drug Liking scores for OXY and PEN were significantly higher compared to PBO ($P<.001$) and SAM (both doses; $P<.001$). Both SAM doses had Emax Drug Liking scores similar to PBO and NAL (median within-subject differences of 0.0). Emax Overall Drug Liking scores were consistent with the primary endpoint. Emax Take Drug Again scores for SAM (both doses) were higher than PBO, but similar to NAL. Common adverse events were nausea, vomiting, and feeling hot.
Conclusions: SAM demonstrated abuse potential similar to NAL and PBO in nondependent, recreational opioid users. The safety profile of SAM was consistent with previous clinical studies.
Supported By: Alkermes, Inc.
Keywords: Abuse Potential, Samidorphan, Opioid Antagonist, Abuse Liability, Recreational Opioid Use

S100. Efficacy and Safety of Brexanolone IV Across Phase 2/3 Studies: A First-In-Class GABAA Receptor Positive Allosteric Modulator for Postpartum Depression

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Background: Postpartum depression (PPD) is a mood disorder that can have serious consequences for the mother and family. Brexanolone iv (USAN; formerly SAGE-547 Injection) showed antidepressant effects in preclinical studies, early Phase 2 studies, and first-ever Phase 3 studies in PPD.
Methods: Three randomized, double-blind, placebo-controlled studies (one Phase 2, two Phase 3) enrolled women $\leq$6 months postpartum, with PPD onset between the 3rd trimester and $\leq$4 weeks postpartum. 17-item Hamilton Rating Scale for Depression (HAM-D) scores were $\geq$26 (Study A and B) or 20-25 (Study C). Subjects received brexanolone iv (90 or

60 μg/kg/hr) or placebo as 60-hour infusions. Assessments were through Day 30.
Results: In Studies A, B, and C, 21, 122, and 104 subjects received study drug. Brexanolone iv 90 μg/kg/hr produced significantly greater mean reductions from baseline in HAM-D at Hour 60 (primary endpoint) than placebo: 21.0 vs. 8.8 Study A, p=0.008; 17.7 vs 14.0 Study B, p=0.025; 14.2 vs 12.0 Study C, p=0.016. Brexanolone iv 60 μg/kg/hr similarly demonstrated a significant reduction (19.9 vs. 14.0; p=0.001). Mean reductions from baseline HAM-D observed with brexanolone iv were durable through Day 30. Secondary endpoints supported the primary results. The safety profile was similar across studies; most common AEs included headache, dizziness, and somnolence.
Conclusions: Rapid and durable (over the study period) reductions from baseline in depressive symptoms were consistently seen across studies, with a generally favorable safety profile. These data support a planned 2018 NDA submission seeking approval as potentially the first pharmacotherapy specifically indicated for PPD.
Supported By: These studies were funded by Sage Therapeutics, Inc.
Keywords: Allopregnanolone, Postpartum Depression, GABA-A, Brexanolone

S101. The Effect of Transdermal Nicotine on Mood and Cognitive Symptoms in Late Life Depression

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Background: Late Life Depression (LLD) is characterized by a poor antidepressant response and by poorer cognitive performance. Preliminary data suggest that nicotine may improve mood in midlife and may improve performance in cognitively impaired populations. We conducted a pilot trial to determine whether transdermal nicotine (TDN) might benefit mood and cognitive performance in LLD.
Methods: Fifteen depressed older adults (14 completers) enrolled in a 12-week open-label trial of TDN. Participation required a > 15 score on the MADRS and subjective cognitive impairment, defined by the Cognitive Complaint Index. Participants were seen every three weeks with TDN titration dependent on tolerability, up to a maximum dose of 21.0 mg/day. Primary outcomes included the MADRS for depression, the Memory Frequency Questionnaire (MFQ) for subjective cognitive complaints, and the Conner's Continuous Performance Task (CPT) for objective cognitive performance.
Results: Thirteen participants were responders (87%) and 8 were remitters (53%; final MADRS < 7). MADRS score decreased over time (slope = -1.51, p-value < 0.001), with a mean change of 18.29 (SD=6.15) and change from baseline at week 3 (Bonferroni-adjusted p-value = 0.0036). MFQ score increased (better performance) over time by 23.64 (SD=40.96, t=2.16, p=0.0500). We did not observe a statistically significant change in the CPT, but did observe improvement in performance on secondary cognition outcomes, including the Cogstate shopping list task (immediate recall; 3.36, SD=5.80, p=0.0486) and the one-back test (working memory speed; -0.04 (0.07), p=0.0494).
Conclusions: Nicotine may be a promising therapy for LLD. However, definitive target engagement and a controlled trial is necessary before clinical usage.
Supported By: K24 MH110598; CTSA award UL1TR000445
Keywords: Geriatric Depression, Nicotine, Clinical-Trial, Cognitive Performance

S102. Pilot Double-Blind, Placebo-Controlled Clinical Trial of Transcranial Alternating Current Stimulation (tACS) for the Treatment of Major Depressive Disorder

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Background: Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders, but recommended pharmacological treatments are associated with suboptimal remission rates and undesirable side effects. Safer and more effective treatments are needed. Here, we evaluated the efficacy and feasibility of transcranial alternating current stimulation (tACS), which we hypothesized would improve clinical symptoms by reducing alpha oscillations in the left frontal regions. (NCT02339285)
Methods: 27 participants were randomized to one of three arms (10Hz-tACS, 40Hz-tACS, or active sham stimulation) and received daily 40 minute sessions for 5 consecutive days. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) was the primary outcome, and change in alpha oscillations as measured by high-density electroencephalography (hdEEG) was the secondary outcome. Exploratory analyses were performed on the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), and Montreal Cognitive Assessment (MoCA).
Results: Although there was no significant interaction between treatment condition (10Hz-tACS, 40Hz-tACS, sham) and session (baseline to four weeks after completion of treatment), exploratory analyses showed that 2 weeks after completion of treatment, significantly more participants in the 10Hz-tACS group were responding in the MADRS and HDRS in comparison to the 40Hz-tACS and sham groups. Furthermore, we found a significant reduction in alpha power over the left frontal regions in EEG after completion of the intervention for only the group that received 10Hz-tACS.
Conclusions: To our knowledge, this is the first clinical trial of tACS for the treatment of MDD. Additional studies with larger sample sizes are needed to better understand the effect of tACS on depression.
Supported By: The research reported in this publication was partially supported by the National Alliance for Research on Schizophrenia and Depression (to F.F., Award 22007). This work was also partially supported by UNC Psychiatry, UNC School of Medicine (to F.F.), the Swiss National Science Foundation (to C.L., grant P300PA_164693), and by the Clinical and Translational Science Award program of the National

Center for Advancing Translational Sciences, National Institutes of Health (Award 1UL1TR001111).
Keywords: Major Depressive Disorder (MDD), Transcranial Alternating Current Stimulation, Clinical Trials, Electroencephalography (EEG)

S103. The International Study to Predict Optimized Treatment in Depression (iSPOT-D): Recent Findings and Future Directions

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Background: The International Study to Predict Optimized Treatment in Depression (iSPOT-D) is a randomized clinical looking at biomarkers of antidepressant treatment outcome in outpatients with non-psychotic Major Depressive Disorder. It is the first to take an integrative neuroscience approach to biomarker discovery, looking across the disciplines of structural and functional MRI, EEG, cognitive performance, and genomics, all in the same patients.
Methods: Since Palmer's (2015) review of treatment predictive biomarkers identified through iSPOT-D, a new wave of results has been published that significantly add to this body of work.
Results: Structural MRI has shown larger hippocampal tail volume predicts remission, while DTI measures of stria terminalis and the cingulate portion of the cingulate bundle predicted non-remission, with a greater specificity for escitalopram and sertraline. A compound "EEG abnormality" biomarker was associated with nonresponse to escitalopram and venlafaxine-XR, but not sertraline, and a slow alpha peak frequency was associated with sertraline response. Early Life Stress (ELS) predicted poor remission, with abuses occurring between ages 4 and 7 years differentially predicting poor sertraline outcome. Furthermore, ELS and amygdala activity interact to differentially predict remission. High BMI's were specifically predictive of venlafaxine-XR remission.
Conclusions: New biomarkers of antidepressant treatment outcome have been identified over the past few years from a range of discipled areas in the iSPOT-D trial. Taking an integrative neuroscience approach to the discovery of these biomarkers, the next step will be to integrate findings across disciplines to enhance prediction accuracy and improve our understanding of the key drivers underlying these relationships.
Supported By: The Brain Resource Company
Keywords: iSPOT-D, Major Depressive Disorder (MDD), Sertraline, Escitalopram, Venlafaxine

S104. Ovarian Steroid Withdrawal Underlies Perimenstrual Worsening of Suicidality: Evidence From a Crossover Steroid Stabilization Trial

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Background: Perimenstrual withdrawal from estradiol (E2) and progesterone (P4) correlates with female risk of suicide attempt. This is the first study to experimentally probe a causal role of E2/P4 withdrawal in perimenstrual exacerbation of suicide risk.
Methods: Participants were females (18-45) with past-month suicidal ideation receiving treatment as usual. Luteal phase confinement of symptoms, chronic medical conditions, pregnancy/breastfeeding, hormone use, and history of mania or psychosis were exclusionary. The study was a crossover double-blind controlled trial of perimenstrual steroid stabilization. Participants received 14 days (starting 7 days following positive urine LH test) of transdermal E2 (.1 mg/day) patches plus oral micronized P4 (100 mg b.i.d.) pills in one condition, and 14 days of placebo patches/pills in the other condition. A washout cycle separated the two counterbalanced conditions. Participants self-reported daily suicidality via smartphone using the Self-Injurious Thoughts and Behaviors Interview.
Results: 27 participants completed both conditions. Blinding was highly successful. The predicted condition $\times$ week interaction (Est=.75, SE=.13, t(703)=5.76, p<.0001) was observed; during placebo, suicidality worsened one-and-a-half person-standard-deviations from the midluteal to the perimenstrual week (Est=1.50, p=.002), and this worsening was prevented during E2/P4 stabilization (Est=.13, p=.89). Further, there was a condition $\times$ week interaction during the medication withdrawal week (Est=-.79, SE=.20, t(703)=-3.95, p<.0001). Delayed E2/P4 withdrawal in the active condition caused a delayed increase in suicidality (Midluteal-to-Withdrawal Week Est=1.34, p=.001) not observed in the placebo condition (Est=.20, p=.77).
Conclusions: Cyclical withdrawal from ovarian steroids appears to underlie established perimenstrual worsening of suicidality. Mediators such as GABAergic neurosteroid withdrawal should be investigated.
Supported By: K99-MH-109667
Keywords: Ovarian Steroids, Suicide, Clinical-Trial, Mood Disorders, Women's Mental Health

S105. Adiponectin Moderates Antidepressant Treatment Response in the CO-MED Randomized Clinical Trial

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Background: Major depressive disorder (MDD) is a complex psychiatric disorder that is often comorbid with metabolic diseases such as obesity, cardiovascular disease, and type II diabetes. A potential link between these disorders is adiponectin, an adipocyte-derived circulating hormone with insulin-sensitizing, anti-inflammatory, and neuroplasticity effects. Reductions in plasma levels of adiponectin have been reported in both humans with depression and in the chronic-defeat mouse model of depression. However, the predictive value of adiponectin for treatment response to depression has not been determined.

Methods: In this report, we investigated the potential moderating effect of baseline adiponectin in patients who provided plasma and were undergoing one of three pharmacological treatments in the Combining Medications to Enhance Depression Outcomes clinical trial (n=160). Improvements with treatment were assessed using changes in the clinician-rated 30-item Inventory of Depressive Symptomatology (IDS-C) from baseline through week 12. We tested for moderator effects using separate pairwise repeated measures mixed-effects models with a treatment arm by adiponectin interaction.
Results: Adiponectin levels did not correlate with baseline depression severity. However, baseline adiponectin levels moderated treatment response between two combination therapies (adiponectin by treatment group by time interaction, $p = 0.029$) Specifically, low adiponectin predicted better response to escitalopram and bupropion than venlafaxine and mirtazapine, whereas high adiponectin predicted better response to venlafaxine and mirtazapine than escitalopram and bupropion.
Conclusions: Antidepressant selection for patients with MDD can be personalized using pre-treatment blood-based biomarkers, such as adiponectin, thereby improving treatment outcomes.
Supported By: N01 MH-90003; R25 MH-101078
Keywords: Adiponectin, Major Depressive Disorder, Metabolic Disorder, SSRI, Bupropion

S106. Acute and Longer-Term Outcomes Using Ketamine as a Clinical Treatment at the Yale Psychiatric Hospital

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Background: Ketamine has emerged as a rapid-acting antidepressant, though controversy remains regarding whether sufficient data exist to justify its use outside of research protocols. In October 2014, our institution began providing ketamine as an off-label therapy for patients not able to participate in research protocols on a case-by-case basis. Here we describe our experience over 30 months providing ketamine as a clinical treatment to participants with severe and treatment-resistant mood disorders.
Methods: Initially, patients were treated with a single- or double-infusion protocol (0.5mg/kg over 40 minutes intravenously). We later transitioned to a 4-infusion protocol over two weeks.
Results: Overall, 54 patients have received ketamine at our institution, with 518 total infusions performed. A subset of 44 patients with mood disorders initiated the four-infusion protocol, of which 45.5% responded and 27.3% remitted by the 4th infusion. A subsample (N=14) have received ketamine on a long-term basis, ranging from 12 to 45 total treatments, over a course of 14 to 126 weeks. We found no evidence of cognitive decline, increased proclivity to delusions, or emergence of symptoms consistent with cystitis in this subsample.
Conclusions: In general, ketamine infusions have been tolerated well. The response and remission rates in our clinical sample were lower than those observed in some research protocols. The small number of patients who have been treated on a maintenance schedule limits the conclusions that can be drawn regarding long-term safety of ketamine, however no long-term adverse effects have been observed in our sample.
Keywords: Depression, Ketamine, Antidepressant, Clinical Trials

S107. Identifying Characteristics of Placebo Responders in Major Depression From the EMBARC Study

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Background: The purpose of the study is to identify individuals with a high likelihood of responding to placebo.
Methods: Data for this report are based on participants of the Establishing Moderators and Biosignatures for Antidepressant Response in Clinical Care (EMBARC) trial who were assigned to the placebo arm (n=141). The elastic net was used to evaluate a total of 283 baseline clinical, behavioral, imaging, and electrophysiological variables in order to identify the most robust set of features that predicted depression severity at week 8 in 100 imputed datasets. Variables that were retained by the elastic net in at least 50% of the imputed datasets were then used in a Bayesian multiple linear regression model to simultaneously predict depression symptom level at exit, the probability of response, and the probability of remission.
Results: Lower baseline depression severity, younger age, absence of melancholic features, absence of history of physical abuse, less anxious arousal, anhedonia and neuroticism, and higher average theta current density in the rostral anterior cingulate predicted higher likelihood of improvement with placebo. The Bayesian model incorporating variables predictive of placebo response was able to predict remission and response with a relatively high degree of accuracy (AUC values of 0.76 and 0.73, respectively), and an interactive calculator using the model was developed.
Conclusions: Easy to measure clinical, behavioral and electrophysiologic assessments can be used to identify responders to placebo with high degree of accuracy. The development of a calculator based on these findings may be

useful in the screening process to reduce placebo response rates.
Supported By: NIMH and NIH (U01MH092221 & U01MH092250)
Keywords: Placebo, Depression, Bayesian Model, Elastic Net

S108. Speed of Remission of Suicidality for Low Amplitude Seizure Therapy (LAP-ST) Versus Right Unilateral Ultra-Brief ECT

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Background: Standard ECT is indicated in many guidelines and some studies for acute remission of suicidality. The effect of a novel form of ECT: low amplitude seizure therapy (LAP-ECT) on suicidality is unknown. The aim of this report is to: 1) Provide an interim/safety analysis of a randomized clinical trial of LAP-ST versus Right Unilateral (RUL) standard ECT (ClinicalTrials.gov ID: NCT02583490), 2) Determine the speed of remission of suicidality between the 2 study conditions.
Methods: Ten patients clinically indicated for ECT in major depressive episodes consented to this study. Patients were randomized to either LAP-ST or standard ECT (both 3 times/week). The scores pertaining to the suicidal ideation (SI) item on the Montgomery Åsberg Depression Rating Scale (MADRS) were analyzed using an independent-sample t-test to compare the 2 arms of the study. SI item remission was defined as clinically non-significant suicidality of 2 or below.
Results: In both groups, suicidality remitted by session 3 on average; and remission occurred for all patients by session 4. There was no significant difference in the SI change score for the LAP-ST group (5.0, SD=1.0) compared to standard RUL ECT group (3.0, SD=1.0) conditions; $t(4)=-2.45$, $p = 0.07$
Conclusions: In this pilot interim analysis, LAP-ST seems safe in terms of having fast remission of suicidality in depressed patients, and the remission was not different than standard ECT. These findings warrant replication in larger clinical trials.
Supported By: Medical College of Georgia at Augusta University
Keywords: Electroconvulsive Therapy, Brain Stimulation, Depression, Suicidality, Safety

S109. Pre-Treatment Body Mass Index (BMI) Differentially Predicts Treatment Outcomes With SSRI Monotherapy and Antidepressant Medication Combinations: Findings From CO-MED Trial

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Background: Recent evidence suggests that body mass index (BMI) may guide selection between antidepressant medications with different mechanisms of action. The purpose of this report is to evaluate if pre-treatment BMI differentially predicts treatment outcomes to currently available antidepressant medications.
Methods: Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants with BMI measurement (n=662) were categorized as normal- or under-weight (<25), overweight (25-<30), obese I (30-<35), and obese II+ (≥35). Logistic regression analysis with remission as the dependent variable and treatment arm-by-BMI category interaction as the primary outcome was used to evaluate if BMI differentially predicted response to escitalopram (SSRI) monotherapy, bupropion-escitalopram combination, or venlafaxine-mirtazapine combination, after controlling for gender and baseline depression severity.
Results: There was a significant treatment arm-by-BMI category interaction (chi-square=12.80, p=0.046) indicating remission rates among the three treatment arms differed on the basis of pre-treatment BMI. Normal- or under-weight participants were less likely to remit with bupropion-SSRI combination (26.8%) than SSRI monotherapy (37.3%, number needed to treat or NNT=9.5) or venlafaxine-mirtazapine combination (44.4%, NNT=5.7). Conversely, obese II+ participants were more likely to remit with bupropion-SSRI (47.4%) than SSRI monotherapy (28.6%, NNT=5.3) or venlafaxine-mirtazapine combination (37.7%, NNT=10.3). Remission rates in the three treatment arms did not differ among overweight and obese I participants.
Conclusions: Antidepressant selection in clinical practice can be personalized with BMI measurements. Bupropion-SSRI combination should be avoided in normal- or under-weight depressed outpatients as compared to SSRI monotherapy and venlafaxine-mirtazapine combination, and preferred in those with BMI≥35.
Supported By: NIMH MH N01-90003, Hersh Foundation
Keywords: Antidepressant Medication, BMI, Inflammation, SSRI, Bupropion

S110. Open Trial of Repetitive Transcranial Magnetic Stimulation in Youth With Treatment-Resistant Major Depression

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Background: Major depressive disorder (MDD) is common in youth and treatment options are limited. We evaluated the effectiveness and safety of repetitive transcranial magnetic stimulation (rTMS) in adolescents and transitional aged youth with treatment-resistant MDD.
Methods: Thirty-two outpatients with moderate to severe, treatment-resistant MDD, aged 13 − 21 years underwent a three-week, open-label, single center trial of rTMS. rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC) using neuronavigation and administered for 15

consecutive weekdays (120% rest motor threshold; 40 pulses over 4 seconds [10 Hz]; inter-train interval, 26 seconds; 75 trains; 3000 pulses). The primary outcome measure was change in the Hamilton Depression Rating Scale (Ham-D). Treatment response was defined as a greater than 50% reduction in Ham-D scores. Safety and tolerability were also examined.
Results: rTMS was effective in reducing MDD symptom severity ($t = 8.94$, $df = 31$, $p < 0.00001$). We observed 18 (56%) responders (greater than 50% reduction in Ham-D score) and 14 non-responders to rTMS. Fourteen subjects (44%) achieved remission (Ham-D score ≤ 7 post-rTMS). There were no serious adverse events (i.e. seizures). Mild to moderate, self-limiting headaches (19%) and mild neck pain (16%) were reported. Participants ranked rTMS as highly tolerable. The retention rate was 91% and compliance rate (completing all study events) was 99%.
Conclusions: Our single center, open trial suggests that rTMS is a safe and effective treatment for youth with treatment-resistant MDD. Larger randomized controlled trials are needed.
Supported By: Alberta Children's Hospital Foundation
Keywords: Adolescent Depression, Repetitive Transcranial Magnetic Stimulation, Dorsal Lateral Prefrontal Cortex, Safety, Tolerability

S111. Randomized, Double-Blind Study of Flexibly-Dosed Intranasal Esketamine Plus Oral Antidepressant Vs. Active Control in Treatment-Resistant Depression

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Background: About 30% of patients with depression fail to achieve remission despite adequate treatment with multiple antidepressants, and are considered to have treatment-resistant depression (TRD).
Methods: This Phase 3, double-blind, active-controlled, multicenter study (NCT02418585), using blinded raters, was conducted at 39 sites in Spain, Germany, the Czech Republic, Poland, and United States from August 2015 to June 2017. The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to ≥ 2 antidepressants in the current episode of depression, with 1 of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed intranasal esketamine (56 or 84 mg twice weekly) and a new oral antidepressant or intranasal placebo and a new oral antidepressant. The primary efficacy endpoint – change from baseline to endpoint (day 28) in Montgomery-Asberg Depression Rating Scale (MADRS) total score – was assessed by mixed-effects model using repeated measures.
Results: 435 patients were screened, 227 randomized, and 197 completed the 4-week double-blind period. Change (LS mean [SE] difference vs. placebo) in MADRS total score with intranasal esketamine/oral antidepressant was superior to oral antidepressant/intranasal placebo at day 28 (-4.0 [1.69], 95% CI: -7.31, -0.64; one-sided $p=0.010$), as well as at earlier timepoints (one-sided $p \leq 0.009$ at 24 hours postdose and days 8 and 22). The most common adverse events reported for esketamine/oral antidepressant were dysgeusia, nausea, vertigo, and dizziness; the incidence of each (20.9-26.1%) was >2-fold higher than for oral antidepressant/intranasal placebo.
Conclusions: Study findings indicate a positive risk-benefit profile of intranasal esketamine, an investigational drug, for treating TRD.
Supported By: Janssen Research and Development, LLC, NJ, USA
Keywords: Esketamine, Ketamine, Treatment Resistant Depression

S112. Does Binge Eating at Baseline Influence Lithium- and Quetiapine-Associated Changes in Anthropometric Measures Over 6 Months of Treatment? Findings From Bipolar Choice

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Background: Lithium and quetiapine can cause weight gain, but their comparative longer term anthropometric effects are unknown, as are moderating effects of baseline binge-eating on such outcomes.
Methods: We assessed 6 month changes in body weight, body mass index (BMI) and waist circumference in 482 adults with DSM-IV bipolar disorders participating in a comparative effectiveness study of lithium versus quetiapine with evidence-based adjunctive treatment (Bipolar CHOICE). Anthropometrics were obtained at baseline, and at 2, 4, 6, 8, 12, 16, 20, and 24 weeks. Binge eating was defined as affirmative responses to MINI items M1 and M3 at baseline. Data were analyzed using a mixed model repeated measures approach, adjusted for baseline values of dependent measures.
Results: Body weight and BMI increased over 6 months with both lithium and quetiapine. However, increases in body weight ($F_{8,3052}=2.9$, $p=0.003$) and BMI ($F_{8,3052}=3.0$, $p=0.002$) were greater with quetiapine. Significant increases in waist circumference were observed only with quetiapine. The relationship between drug treatment and changes in body weight ($F_{1,2770}=2.0$, $p=0.002$), BMI ($F_{1,2767}=2.0$, $p=0.002$),

and waist circumference (women only, $F25,1621=2.9$, $p<0.0001$) were moderated by baseline binge eating. Greater waist circumference increases occurred in women ($F25,1621=2.6$, $p<0.0001$), but not men, in the quetiapine group for binge eaters (versus non-binge eaters), and lower increases in body weight/BMI were observed in the lithium group for non-binge eaters.

Conclusions: Lithium- and quetiapine-based treatments were associated with longer-term anthropometric adverse effects. Baseline binge eating may cause more severe weight gain risk in treated patients.

Supported By: Agency for Healthcare Research and Quality (AHRQ): 1R01HS019371

Keywords: Bipolar Disorder, Lithium, Quetiapine, Weight Gain, Body Mass Index

S113. Unintended Discontinuation of Deep Brain Stimulation for Treatment-Resistant Depression: A Case Series

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Background: Deep brain stimulation (DBS) of the medial forebrain bundle (slMFB) for treatment-resistant depression (TRD) is currently under research. Rapid and sustained antidepressant effects over five years have been demonstrated. The effect of an unintended discontinuation of DBS (e.g., due to battery depletion) after chronic stimulation has not been evaluated yet.

Methods: Four cases with an unintended interruption of stimulation are reported. In one case (#5), stimulation was intentionally discontinued for four days and Montgomery-Åsberg-Depression-Rating Scale (MADRS), Hamilton-Depression-Rating Scale (HDRS) and Beck-Depression-Inventory (BDI) were assessed.

Results: All patients experienced depressive symptoms directly after the discontinuation of stimulation. In case 5, depressive symptoms significantly increased from remission (MADRS = 1; HDRS = 1; BDI = 4) to moderate depression (MADRS = 12; HDRS = 12; BDI = 9). After reinitiation of DBS, time to antidepressant response varied. In case 5, symptoms disappeared after the re-onset of stimulation and remained remitted until the last follow-up (MADRS = 0; HDRS = 0; BDI = 0).

Conclusions: This is the first case of a planned discontinuation of DBS in a controlled setting after long-term DBS of the slMFB. Together with a case series of four patients with unintended discontinuation of stimulation, continous DBS for the treatment of TRD seems necessary. This finding is in line with effects of DBS in Parkinson's disease and suggests that DBS only leads to transient changes in brain functioning. An accidental discontinuation should be regarded as a safety aspect because of the rapid return of symptoms after only one day.

Supported By: This investigator-initiated study was funded in part (DBS device, battery exchange, medical costs, and limited support for study nurse) by a grant of Medtronic Inc. to Prof. Schlaepfer and Prof. Coenen. All other authors state no conflict of interest.

Keywords: Deep Brain Stimulation, Treatment-Resistant Depression, Medial Forebrain Bundle, Discontinuation of DBS

S114. Efficacy and Safety of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression

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Background: This double-blind phase 3 study (NCT02422186) evaluated the efficacy and safety of intranasal esketamine (ESK) in elderly patients with treatment-resistant depression.

Methods: Patients ≥65 years (N=138) were randomized (1:1) to either ESK + oral antidepressant (AD) or AD + placebo (PBO). The primary efficacy endpoint − change from baseline to day 28 in Montgomery−Åsberg Depression Rating Scale (MADRS) total score − was assessed by mixed-effects model at a one-sided 0.025 significance level. Pre-specified subgroup analyses were performed for 65-74 years (n=116) and ≥75 years (n=21). Remote raters, blinded to the treatment arm, conducted the MADRS assessments by telephone.

Results: The mean (SD) change in MADRS total scores from baseline to day 28 was -10.0 (12.74) for ESK+AD and -6.3 (8.86) for AD+PBO. The median-unbiased estimate of the difference between ESK+AD and AD+PBO was -3.6 (95% CI: -7.20, 0.07; one-sided p=0.029). A treatment difference favoring ESK+AD was seen for the 65-74 years subgroup. The difference in LS mean (SE) change at day 28 was -4.9 (2.04) for 65-74 years (one-sided p=0.009) and -0.4 (5.02) for ≥75 years (one-sided p=0.465). Most common treatment-emergent adverse events (TEAEs) in the ESK+AD group were dizziness (20.8%), nausea (18.1%), headache (12.5%), fatigue (12.5%), increased blood pressure (12.5%), vertigo (11.1%) and dissociation (11.1%). Most common TEAEs in the AD+PBO group were anxiety, dizziness and fatigue (7.7% each).

Conclusions: While treatment with ESK+AD did not demonstrate a statistically significant difference vs AD+PBO on the primary outcome, a statistically significant and clinically meaningful treatment effect was observed for patients aged 65-74 years.

Supported By: Janssen Research & Development, LLC

Keywords: Esketamine, Treatment-Resistant Depression, Elderly, Ketamine

S115. Cortical Reserve Predicts Response to Cognitive Remediation in Bipolar Disorder

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Background: Cognitive dysfunction is a core symptom dimension in bipolar disorder, and a strong predictor of functional outcomes. Cognitive remediation (CR) produces significant, durable effects on cognition in patients with schizophrenia (SZ) (Wykes et al., 2011) and bipolar disorder (BD) (Lewandowski et al., 2017). However, not all patients respond robustly to CR. "Cortical reserve" may predict response to CR in patients with SZ (Keshavan et al., 2011); this association has not been tested in BD. We examined the effects of baseline cortical reserve on CR treatment response in patients with BD.
Methods: Patients with BD were randomized to a 24-week CR or a dose matched active control. Patients who received an MRI scan at baseline (n=34) were included in this report. We examined total intracranial volume (eICV) and total brain volume (TBV) as measures of cortical reserve. Cognitive and clinical assessments were administered at baseline and post-treatment. Responders were defined using a 90% CI of composite change method (Gasto, 2006).
Results: Groups differed on proportion of responders (CR = 75%; Control = 33%). Comparison of baseline structural measures showed significantly reduced eICV and TBV in non-responders ($F(1, 20) = 7.84$, $p = 0.01$ and $F(1, 20) = 7.62$, $p = 0.01$, respectively. After controlling for sex, age, and baseline cognition these findings remained unchanged.
Conclusions: Given the lengthy and intensive nature of CR programs and the unmet need for cognitive treatments in psychosis, identifying predictors of treatment response will allow selection of candidates likely to benefit from treatment and individualized tailoring of treatments to best meet patients' needs.
Supported By: K23MH091210
Keywords: Cognitive Remediation, Bipolar Disorder, Brain Imaging, fMRI, Prediction of Treatment Outcome

S116. The Use of Arterial Spin Labeling Perfusion MRI for Automated Classification of Major Depression Disorder

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Background: In recent years, neuroimaging based multivariate pattern recognition methods have been successfully implemented to develop diagnostic algorithms to distinguish patients with major depressive disorder (MDD) from healthy controls (HC) at the individual level. The objective of this study was to examine the accuracy of a high-level machine learning model for classification of MDD and HC using cerebral blood flow (CBF) measured using non-invasive arterial spin labeling (ASL) magnetic resonance imaging.
Methods: Twenty-two medication-free patients with the diagnosis of MDD based on DSM-IV criteria and 22 HC underwent a non-contrast pseudo-continuous 3D-ASL scan to determine regional CBF measurements in the brain. A support vector machine (SVM) based feature selection method was employed to select the optimal feature set. Following this step, individual level differentiation of MDD and HC was performed using a linear kernel SVM.
Results: The automatic classification based on ASL-perfusion data revealed a statistically significant accuracy of 77.3% ($p = 0.004$) with a specificity of 80% and sensitivity of 75%. Occipital cortex, prefrontal and cingulate cortices, and brain stem were ranked as the most differentiating features between the two groups.
Conclusions: This is the first work showing that machine learning methods based on ASL perfusion measures are capable of differentiating MDD from HCs on an individual level. The use of larger datasets in combination with other imaging modalities may improve classification performance of the classifier to achieve the accuracy required for clinical applications.
Keywords: Depression, Arterial Spin Labeling, Machine Learning

S117. Dorsolateral Prefrontal Cortex Activity is Impaired in Currently-Depressed Patients, but Intact in Individuals at High Risk

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Background: The neural mechanisms affecting risk for and resilience to depression are largely unknown. Neuropsychological models of depression posit that negatively biased emotional ("hot") processing confers risk for depression, while preserved non-emotional ("cold") cognition might promote resilience. However, no studies have compared samples at high-risk for depression and those currently experiencing a major depressive episode on neural responses during hot and cold cognition.
Methods: We recruited 99 participants: 39 unmedicated currently-depressed patients, 30 unaffected first-degree relatives of depressed individuals, and 30 age- and sex-matched healthy controls with no first-degree relatives with depression. Using functional magnetic resonance imaging we assessed neural responses on two tasks previously associated with depression. Dorsolateral prefrontal cortex (DLPFC) responsivity was assessed during the N-back working memory task; and amygdala and subgenual anterior cingulate cortex (sgACC) responsivity were assessed during incidental emotional face processing.
Results: There was a main effect of group on DLPFC activation ($p = 0.013$), such that unaffected relatives did not differ significantly from healthy volunteers on DLPFC activation during working memory ($p = 0.923$), while depressed patients exhibited significantly attenuated activation compared to both

healthy controls (p=0.024) and unaffected relatives (p=0.007). We did not observe a complementary pattern on the emotion processing task. However, DLPFC activation was inversely related with amygdala activation across all participants (p=0.039).
Conclusions: These findings have important implications for understanding the neural mechanisms of risk and resilience in depression. Specifically, they are consistent with the proposal that preserved cold cognitive function may confer resilience to depression in at-risk individuals. However, this requires confirmation in longitudinal studies.
Supported By: Brain Research Trust; NARSAD
Keywords: Dorsolateral Prefrontal Cortex, Depression, Brain Imaging, fMRI, Resilience, Mood Disorders

S118. Emotional Memory Changes and its Correlation With Severity in Bipolar Disorder

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Background: Emotional memory (EM) is a type of memory which requires emotional arousal for acquisition and consolidation. EM is highly dependent of amygdala function and, therefore, the assessment of an abnormal EM in Bipolar Disorder (BD) could indirectly indicate disfunctional hyperactivation of the amygdala. This study aims to correlate EM changes in BD with severity of disease.
Methods: Thirty-three BD and 20 paired Healthy Controls (HC) completed clinical questionnaire and EM scale. The EM assessment consisted of 20 lists of 12 words each, including Emotional (E), E-1 (precedes E), E+1 (follows E), Perceptual (P), P-1 (precedes P), P+1 (follows P) and Control (C). Participants should mention all recalled words from each list. T-test assessed which subject group had better general recall. Generalized estimating equations (GEE) assessed influence of diagnosis, of type and position of words in recall, and of number of previous mood episodes (NME).
Results: HC showed a better general recall of words than BD (52.05 ±15.33 vs.34.06 ±15.92, p<0.001). In statistical models, there was a significant fit only for group difference: BD showed an increased EM score despite of type or position of the word (p=0.008). When we added NME to the model, there was an association with EM (p=0.042). Correlation between EM and NME was significant (r=-0.324, p<0.001).
Conclusions: BD showed an enhanced memory for items either with negative valence or perceptual difference and for those words that surrounded them. This enhancement seems to decline with NME. Amygdala activation and function may be a promising marker of stages in BD.
Supported By: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES);

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Keywords: Amygdala, Emotional Memory, Clinical Staging, Bipolar Disorder, Cognition

S119. Prospective Predictors of Suicidal Behavior in Old Age

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Background: Neurocognitive and decision-related factors may play a particularly important role in late-life suicide due to age-related cognitive decline. While case-control retrospective studies have implicated cognitive and decision-making deficits in late-life suicidal behavior, prospective evidence is lacking.
Methods: We examined the prospective relationship between clinical and cognitive/decision-making factors with incident suicidal behavior (median follow-up: 5.4 years) in 311 non-demented depressed older adults (age: 65.6 ±9.8); 153 with prior attempts, 71 with suicidal ideation only, and 83 non-suicidal depressed, while 90 non-psychiatric controls served as a benchmark group. Competing risk models were used to predict risk of suicidal behavior, accounting for censoring of the observations of suicidal behavior by death from other causes.
Results: Of the 401 participants, 76 died during study follow-up, 9 by suicide. Twenty-eight participants had at least one suicide attempt during follow-up, of whom 15 made high-medical-lethality attempts. For the combined outcome of high-lethality attempts or death by suicide, significant predictors included impaired cognitive control (p=0.002) and decision competence deficits (susceptibility to framing, p<0.001), family history of death by suicide (p<0.001), depression severity (p=0.006), lower non-planning impulsivity (p=0.041), male sex (p=0.009), higher per capita income (p=0.003), and anticipation of shorter life expectancy (p=0.044). For low-lethality attempts, predictors included interpersonal difficulties (p=0.007), lower premorbid intelligence (p=0.037), higher negative (p<0.001) and positive (p=0.008) urgency, current substance abuse (p=0.003), lower extraversion (p=0.039).
Conclusions: In late life, cognitive/decision-making deficits are associated with serious suicidal behavior, while dysfunctional personality traits, such as impulsivity and interpersonal dysfunction, predict less serious suicide attempts.
Supported By: NIMH R01MH085651
Keywords: Prospective Prediction, Suicide, Near-Fatal Attempts, Cognitive/Decision Processes, Personality

S120. Canadian Biomarker Integration Network in Depression (CAN-BIND): Baseline and Follow up Neurocognitive Mediators of Functioning in Major Depressive Disorder (MDD)

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Background: This study examined cognitive performance and functioning in untreated depressed patients assessed at baseline and following treatment with an antidepressant after 8 weeks.
Methods: The CANBIND (Canadian Biomarker Integration Network for Depression) study assessed cognition using CNS (Central Nervous System) Vitals as well as functional measures at baseline and again at 8 weeks. Functioning was assessed by the Sheehan Disability Scale (SDS) and Lam Employment, Absence and Productivity Scale (LEAPS). All patients received escitalopram (10-20mg) for 8 weeks while healthy controls received placebo.

We hypothesized that patients (n=184) would greater baseline deficits in cognition relative to healthy controls (n=95) and that improvements in cognition would be associated with a greater degree of functional improvement.
Results: Baseline cognitive impairment was evident in the depressed sample with the domains of composite memory, psychomotor speed, complex attention and cognitive flexibility statistically significantly impaired relative to controls. No baseline cognitive measure was correlated with baseline functioning. In linear regression modeling, baseline depression severity (t=4.5, p=0.0001) and baseline reaction time (t- -2.2, P=0.03) predicted baseline LEAPS score while baseline composite memory predicted baseline disability. Severity of depressive illness correlated with neuropsychological impairment. Cognition improved over the 8 week period. Improvement in psychomotor speed was correlated with improved work productivity (r= -.03, P=0.01) but not disability in patients.
Conclusions: Cognition improved in depressed patients following antidepressant treatment and individual domains were associated with increased productivity and less functional disability. Future research will focus on how antidepressant augmentation could provide additional benefits to productivity and functioning.
Supported By: Ontario Brain Institute (OBI), Ontario, Canada.
Keywords: Depression, Cognition, Antidepressant Response, Cognitive Dysfunction, Role Functioning

S121. Measures of Behavior and Life Dynamics From Smartphone GPS Data

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Background: Locations of people moving through the world are now available through GPS data. While most studies use such data for navigation and activity measurement, here we investigate derived measures that estimate life patterns captured by extracting returns to locations in meaningful time bands (e.g., during late night sleep or evening social epochs). The top ranked locations visited were extracted from continuous location data. By estimating the time spent in those locations across the meaningful time bands, measures of behavioral dynamics and social interactions were gleaned.
Methods: GPS data from 50 college students (for 90-140 days) and 9 individuals with bipolar disorder or schizophrenia spectrum (for 100-400 days) were collected using Beiwe, a research platform for smartphone-based digital phenotyping. The GPS locations were collected every 20 min; epoch-based data processing and density-based clustering techniques were developed and used to detect locations of interest. Markov Chain models were used to quantify transitions among locations.
Results: Individuals have unique patterns of spending time at their locations of interest during meaningful epochs of work, social life, nightlife, and sleep. Markov Chain models show that the individuals can be categorized into several behavioral phenotypes according to their sleep and nightlife patterns. Moreover, there are indications of idiosyncratic behavioral and life patterns in individuals with psychiatric illness.
Conclusions: Measures derived from temporally constrained time epochs of smartphone GPS data provide a new window into clinically relevant behavior collected continuously in the real world.
Supported By: NIH DA022759, MH103909, MH104515, Ellison Foundation, and Kent and Liz Dauten, 1P50MH106435
Keywords: Behavior and Life Dynamics, Digital Phenotyping, GPS Data Analysis, Mood Disorder, Epoch-based Analysis

S122. Behavioral and Neural Alterations in Competitive Behavior in Major Depressive Disorder

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Background: The social defeat model of depression suggests individuals with depression are more likely to exhibit diminished competitive behavior within social contests. Here, we combine computational models of social behavior and functional neuroimaging to examine how valuation of social status and neural mechanisms of guilt contribute to alterations in competitive behavior among individuals with major depressive disorder (MDD).
Methods: Sixty-five participants with MDD (40 females, age: 34.7±11.2) and 47 matched non-psychiatric controls (30 females, age: 32.7±10.5) played a multi-round resource contest game with a computer opponent. In a given trial, a 'alpha' player first decided to transfer a portion of a monetary endowment to a 'beta' player. A social contest occurred if 'beta' decided to challenge, and the two players competed for the next round's alpha position. A hierarchical Bayesian model including two parameters of interest, i.e. guilt and preference for dominance, was fit to the observed behavioral choices.

Results: Behaviorally, MDD participants made more high-value transfers (p=.04) and challenged opponents as often as controls (p=0.48). Model estimation suggested higher guilt in MDD (p=.02), which positively correlated with depressive symptoms (p=.008), and comparable preference for dominance between the two groups (p=.68). Neurally, MDD participants showed intact striatal response to winning. Greater guilt was associated with transfer-associated activity in ventral medial prefrontal cortex and greater response of bilateral anterior insula to challenges.
Conclusions: Enhanced guilt, combined with intact valuation of social status, suggests alterations in competitive behavior and associated neural mechanisms among depressive individuals may be attributable to a preference for equitable division of resources.
Supported By: National Institutes of Health (DA036017 to BKC, MH087692 to PC)
Keywords: Major Depressive Disorder (MDD), Computational Psychiatry, fMRI, Social Behavior

S123. Could Response Inhibition Impairment be a Biomarker of Atypical Depression? Differential Cognitive Impairment Profile in Atypical, Treatment-Resistant Depression

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Background: Major Depressive Disorder (MDD) is a heterogeneous disorder. Cognitive deficits may function as a behavioral biomarker, aiding to improve diagnosis of subtypes of depression. Few studies have investigated the neuropsychological performance of MDD patients in subgroups of refractory MDD.
Methods: We examined a sample of unipolar, treatment-refractory-MDD patients for cognitive impairments. A neuropsychological battery was administered, using measures of verbal learning and recall (RAVLT), verbal fluency (COWA), attention (TMT), inhibition (Stroop), and working memory (SJS). We compared all patients (TRD) to healthy controls (HC). We compared patients with, to patients without, comorbid anxiety disorders. We compared performance in patients with, and without, atypical depression. We ran ANOVAs to compare the neuropsychological performance between patient groups and healthy controls.
Results: There was a significant difference in the neuropsychological performances between TRD (n=62) and HC (n=40) in three domains. TRD performed worse in measures of recall (p<0.05), attention (p<0.001), and inhibition (p<0.05). TRD patients with comorbid anxiety disorders (n=20) were not significantly more impaired than patients without comorbid anxiety disorders (n=42). Patients with atypical TRD (n=17) performed worse than patients without atypical TRD (n=45) on measures of inhibition. While this difference was not statistically significant, there was a sufficient effect size (Cohen's d=1.36).
Conclusions: We conclude that patients with TRD show impaired cognitive functioning in domains of recall, attention, and inhibition. TRD patients with atypical depression may be more impaired in inhibition as compared to those without atypical depression. This difference in cognitive profiles may lead to improvement in differential diagnosis of depression.
Keywords: Treatment Refractory Depression, Cognitive Impairment, Atypical Depression

S124. Differences in Cognitive Control Brain Activation Between Euthymic Bipolar and Remitted Unipolar Depressed Individuals

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Background: Dysregulation of cognitive function is known to occur in bipolar mood states and vestiges persist through to euthymia. The same has been shown in both symptomatic and remitted major depression. Hence this study investigated potential differences in the neural substrates of persistent cognitive dysfunction in euthymic/remitted bipolar and unipolar depressed populations by comparing brain activation during response inhibition.
Methods: 23 euthymic bipolar (eBP), 23 remitted major depressive disorder (rMDD) and 23 healthy control (HC) participants, matched on age and sex, completed a functional magnetic resonance imaging (fMRI) task measuring response inhibition (Go-NoGo). Brain activations in ROIs of the cognitive control brain network (bilateral dorsolateral prefrontal, posterior parietal cortices and the dorsal anterior cingulate) for NoGo vs Rest (baseline) were analyzed in SPM8 and compared between groups, at a cluster-level FDR of $p < 0.05$, $k > 71$ voxels.
Results: Euthymic BP patients had significantly greater activation in bilateral inferior and superior posterior parietal cortices compared to rMDD patients ($p = 0.001$) and in the left superior posterior parietal cortex compared to HC participants ($p = 0.011$). Healthy controls had increased right-sided dorsolateral prefrontal ($p = 0.018$) and parietal cortex activation compared to the rMDD group ($p < 0.013$).
Conclusions: Heightened posterior parietal activation during response inhibition can differentiate euthymic bipolar disorder patients from both remitted depressed patients and healthy controls. These findings suggest that fMRI brain measures can be used to identify trait-specific markers that in turn

characterize and thus potentially distinguish bipolar and unipolar depression largely independent of illness state.
Supported By: NHMRC
Keywords: Bipolar Disorder, Unipolar Major Depression, Cognition, fMRI

S125. Different Definitions Reflect Neurobiologically Distinct Subtypes of Depression

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Background: Major depressive disorder (MDD) is a debilitating psychiatric disorder with the key symptom of low mood, but can be more specifically defined in different ways. Recent evidence indicates that various definitions relate to the same genetic basis, suggesting each reflects the same disorder. We investigated whether this was supported by neurobiological measures, specifically cortical structure.
Methods: We tested associations between MDD and regional cortical metrics, and whether associations depended on MDD definition, among 3,867 UK Biobank participants. Eight MDD definitions were derived from a variety of instruments, ranging from self-report to more strict clinical criteria. Cortical metrics were extracted from FreeSurfer output, following quality control. Associations and interactions were tested using linear regression and reversed generalised mixed models.
Results: Mean absolute β coefficient for MDD-cortex associations was between .02 and .04 for most definitions, but around .08 for hospital records of MDD. Mixed model analyses confirmed significant interactions between MDD status and definition for the majority of regions, up to $\chi 2=53.93$ for surface area of the left supramarginal gyrus. Many interactions remained significant after FDR correction, consistently across hemispheres and metrics for several frontal and parietal regions, as well as lateral occipital cortex.
Conclusions: Associations between MDD and cortical metrics were generally weak, yet clearly dependent on MDD definition. These results suggest different definitions could reflect different subtypes or facets of MDD, relating to cortical structure in different ways. It is therefore important to consider how MDD is operationalised when analysing or interpreting neurobiological associations.
Supported By: Wellcome Trust; UK Medical Research Council
Keywords: Major Depressive Disorder (MDD), Brain Cortex, Brain Imaging, Subtypes

S126. Association Between Suicidal Ideation and Cortical Volume in a Sub-Clinical Sample of Young Individuals

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Background: Suicide is one of the leading causes of death among 15-29 years old individuals and approximately 800,000 people die due to suicide every year. A better understanding of the neuroanatomical basis of suicidal ideation (SUI) remains an important challenge in ongoing attempts to understand and treat this psychiatric disorder.
Methods: We recorded neuroanatomical data from 55 psychiatrically healthy young participants (i.e., did not meet the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for Axis-I mental disorders). The Personality Assessment Inventory (PAI), including the SUI (PAI-SUI) and depression (PAI-DEP) subscales, was administered to each individual. The FreeSurfer toolbox was used to identify clusters showing significant associations between cortical volume (CV) and PAI-SUI outcomes at a cluster-forming threshold of $p < 0.001$ (corrected for multiple comparisons), while controlling for age, sex and PAI-DEP.
Results: We observed a significant negative association between PAI-SUI and CV in three clusters including the left pars orbitalis, the left superior temporal gyrus, and the right lateral occipital cortex.
Conclusions: Our findings indicated that even for healthy individuals who do not meet the DSM-IV criteria for Axis-I mental disorders, increasing levels of SUI are associated with decreases in CV within several critical brain regions. These areas should further be investigated as potential SUI biomarkers to better understand the basis of neuropathophysiology of suicidal behavior in suicidal attempters. It will be important for future studies to establish the relationships between neuroanatomical and suicidal ideation in a larger sample that includes a representative range of psychiatric distress.
Supported By: USAMRMC W81XWH-09-1-0730
Keywords: Suicidal Ideation, Cortical Volume, Structural Neuroimaging

S127. Systemic Inflammation is Associated With Stronger Coupling Between Striatum Activity and Food Pleasantness Ratings in Depression With Appetite Loss

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Background: Depression-related appetite changes are indicative of underlying inflammatory, metabolic, endocrine, and neural differences among distinct subtypes of major depressive disorder (MDD). For example, Penninx and colleagues (e.g. Lamers, 2013) have shown that depression accompanied by increased appetite is associated with heightened systemic inflammation, and Simmons and colleagues (2016) have observed differential reward-circuit

activity to food cues in depressed subjects with increased and decreased appetite. It remains unclear, however, how inflammation in specific depression subtypes might ultimately alter activity of neural systems that select when, what, and how much to eat. To address this question, we examined how C-Reactive Protein (CRP) levels affect the relationship between brain activity and participants' predictions about how pleasant it would be to eat specific foods.

Methods: 64 unmedicated participants (33 healthy control (HC), 17 MDD with decreased appetite, and 14 MDD with increased appetite) provided a blood assay for CRP and completed a food pleasantness rating fMRI task. Groups were matched for age, and the MDD subgroups did not differ in depression severity or anxiety. Imaging data was analyzed using amplitude modulation regressors to account for subjects' unique ratings of food pleasantness.

Results: MDD participants with appetite loss provided lower food pleasantness ratings than MDD participants with increased appetite ($p < 0.05$). Additionally, in MDD participants with appetite loss, higher CRP was associated with stronger coupling between food pleasantness ratings and activity of the ventral striatum.

Conclusions: Systemic inflammation alters the coupling between striatum activity and food pleasantness inferences in depressed subjects with appetite loss.

Supported By: National Institute of Mental Health (K01MH096175-01) and National Institute of General Medical Sciences Center Grant (1P20GM121312)

Keywords: BOLD fMRI, Major Depression, Appetite, Inflammation, C-Reactive Protein

S128. Predicting Individual Responses to the Electroconvulsive Therapy With Hippocampal Subfield Volumes in Major Depression Disorder

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Background: Electroconvulsive therapy (ECT) is one of the most effective treatment for major depression disorder (MDD). ECT can induce neurogenesis and synaptogenesis in hippocampus, which contains distinct subfields, e.g., the cornu ammonis (CA) subfields, a granule cell layer (GCL), a molecular layer (ML), and the subiculum. It is still unclear which of these subfields are affected by ECT in MDD. More importantly, can we predict the future treatment response to ECT by using volumetric information of hippocampal subfields at baseline?

Methods: In this study, 24 patients with severe MDD received the modified ECT and their structural brain images were acquired with magnetic resonance imaging before and after ECT. A state-of-the-art hippocampal segmentation algorithm was used.

Results: We found that ECT induced volume increases in CA subfields, GCL, ML and subiculum. We applied a machine learning algorithm to the hippocampal subfield volumes at baseline and were able to predict the change in depressive symptoms at the individual level ($r=0.81$). Within the remitters, the degree of alleviation of depressive symptoms by ECT could be predicted with high accuracy ($r=0.93$). Receiver operating characteristic analysis also showed robust prediction of remission with an area under the curve of 0.90.

Conclusions: Our findings provide evidence for particular hippocampal subfields having specific roles in the response to ECT treatment in MDD. We also provide an analytic approach for generating predictions about clinical outcomes for ECT in MDD using hippocampal subfield volumes and machine learning methods.

Supported By: R01 085667; NARSAD

Keywords: Electroconvulsive Therapy (ECT), Major Depressive Disorder (MDD), Treatment Response, Hippocampal Subfields

S129. Disrupted Noradrenergic Connectivity in Patients With Late-Life Major Depression

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Background: The Locus Coeruleus (LC) is the major source of noradrenergic neurotransmission, targeting different cortical and subcortical brain regions. Structural alterations of the LC have been observed in neurodegenerative and psychiatric disorders. However, fewer studies have evaluated functional alterations. Here we aimed to investigate LC activity and connectivity during performance of an attentional task in patients with late-life major depression (MD) and patients with mild cognitive impairment (MCI).

Methods: We assessed 20 patients with MD (mean age±SD=67.05±0.96), 16 patients with MCI (mean age±SD=71.13±0.71), and 26 healthy controls (mean age±SD=67.42±0.85). All participants underwent a functional magnetic resonance assessment during the performance of a visual oddball task. Participants also underwent a T1-weighted neuromelanin-sensitive sequence for LC localization. We assessed task-related activations and modulation of connectivity with other brain areas (i.e., Psychophysiological Interactions).

Results: We did not observe significant across-group differences in brain activations. Conversely, MD patients, in comparison with the other two groups, showed lower global connectivity degree during oddball detection in a cluster encompassing the right caudal LC ($t=3.20$). Specifically, MD patients showed a reduced connectivity between the LC and the right fusiform gyrus, the left cerebellar hemisphere and the left anterior cingulate cortex (ACC). Connectivity between the LC and the ACC correlated negatively with Geriatric

Depression Scale scores (r=-0.48) and the number of previous depressive episodes (r=-0.55).
Conclusions: Reduced connectivity of the LC with the ACC during performance of an attentional task seems to specifically characterize patients with late-life MD, and is associated with severity and longitudinal course of the disorder.
Supported By: Carlos III Health Institute (PIE14/00034, CPII16/00048) & Feder Funds, a way to build Europe.
Keywords: Functional Brain Imaging, Locus Coeruleus, MCI, Brain Connectivity, Late Life Depression

S130. Dissecting the Neuroimaging Phenotype of Major Depressive Disorder Based on Genetic Loading for Schizophrenia

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Background: Major depressive disorder (MDD) is a heritable, disabling psychiatric disorder, defined by the presence of an arbitrary number of symptoms. Such syndromal definitions are likely to group individuals with diverse aetiologies. MDD shares symptoms, risk genes, and brain imaging findings with other psychiatric disorders, such as schizophrenia (SCZ). Here, we tested the hypothesis there may be a differential association between imaging measures and genetic risk for schizophrenia in MDD cases versus controls, which may indicate a SCZ-risk-driven aetiological subtype of MDD.
Methods: We used UK Biobank subjects with genetic, clinical and neuroimaging data (n=6,981). Imaging measures included subcortical volumes, measures of white matter microstructure, and a subset with locally-derived cortical measures (n=2,967). We implemented standard linear regression models to examine associations between SCZ polygenic risk score (SCZ-PGR) and imaging measures in the presence/absence of depression.
Results: We observed a significant SCZ-PRS by MDD-status interaction for the mean cortical thickness (CT) of the rostral anterior cingulate cortex (ACC, β=0.19, pcorr=0.004). This was driven by a significant negative relationship in controls (β=-0.09, pcorr=0.031), with no significant relationship in cases (β=0.10, pcorr=n/s). Maximal group differences occurred at lower SCZ-PRS scores, with convergence at higher SCZ-PRS.
Conclusions: While we demonstrated significant SCZ-PRS x group (MDD-status) interactions in the rostral ACC, this was not driven by MDD cases at high SCZ-PRS. The absence of the negative SCZ-PRS/CT associations in cases, that was seen in controls, may indicate differential aetiological mechanisms contributing to reductions in CT in this region in those at low SCZ-PRS with MDD.
Supported By: Wellcomte Trust, Royal College of Physicians of Edinburgh
Keywords: Depression, Anterior Cingulate Cortex (ACC), Cortical Thickness, Polygenic Risk Score, Schizophrenia

S131. Resting State Functional Connectivity Patterns Differentially Predict Treatment Outcomes to Sertraline Versus Placebo in Patients with Major Depressive Disorder

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Background: The purpose of this report is to identify if alterations in connectivity of brain regions involved with emotion processing (amygdala), executive function (dorsolateral prefrontal cortex, DLPFC) and reward processing (ventral striatum, VS) with other brain regions in patients with major depressive disorder (MDD) predict differential outcome to sertraline versus placebo.
Methods: Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study participants who completed structural and resting state functional magnetic resonance imaging (rsfMRI) at baseline and were randomized to either sertraline or placebo for 8 weeks were included (n=279). Separate voxel-wise mixed model analyses for seed-based (bilateral amygdala, DLPFC, and VS) functional connectivity were used to identify connectivity patterns which differentially predicted outcomes between sertraline and placebo (moderators). Effect sizes (ES) were estimated for each moderator, and remission rates were calculated based on quartiles of moderators with ES>0.20.
Results: Higher resting-state functional connectivity of right thalamus−amygdala (ES=0.23), left precuneus−amygdala (ES=0.22), left and right precentral−DLPFC (ES=0.20,0.20), left medial frontal−DLPFC (ES=0.20), and left middle temporal−VS (ES=0.22), and lower functional connectivity of left medial frontal gyrus (L)−VS (ES=0.26) and left middle frontal gyrus−VS (ES=0.21) predicted better outcomes with sertraline versus placebo. Remission rates greatly differed in participants in top quartile of right thalamus−amygdala (sertraline=54.6%, placebo=18.2%; NNT=2.75) and left precuneus−amygdala (sertraline=51.2%, placebo=15.2%; NNT=2.75) connectivity.
Conclusions: Functional connectivity patterns of brain regions involved in emotion processing, executive function, and reward processing differentially predict outcomes to antidepressant medications versus placebo and can be used to personalize MDD treatment.
Supported By: U01MH092221; U01MH092250

Keywords: Major Depressive Disorder (MDD), Functional Connectivity, Prediction of Treatment Outcome, Biomarkers, Functional Neuroimaging

S132. Cerebral Blood Perfusion Predictors of Antidepressant Response in Major Depressive Disorder

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Background: Cerebral blood flow (CBF; perfusion), as measured by Arterial Spin Labeling (ASL) has been used to understand brain function as well as detect abnormalities and treatment-related differences in Major Depressive Disorder (MDD). CBF could potentially serve as a predictor of treatment response, which is the aim of the current work.
Methods: Baseline ASL scans were acquired on 231 MDD participants in the Establishing Moderators/Biosignatures of Antidepressant Response in Clinical care study to identify biomarkers of treatment response. Participants were randomized to Sertraline (SERT; n=114) or Placebo (PBO; n=117) and monitored for 8-weeks. Relative-CBF (rCBF) was entered into a whole-brain, voxel-wise linear mixed-effects model (FDR-corrected $p<.05$) to identify rCBF predictors, moderators, of outcome.
Results: rCBF moderators of outcome were identified in the inferior, middle, and superior frontal gyri, inferior and middle temporal gyri, fusiform, parahippocampus, anterior cingulate and calcarine cortices, thalamus, and caudate, all $z>2.63$, $p<.01$. SERT given to those with low-rCBF in the thalamus, caudate, inferior and middle frontal gyri resulted in greater decreases in MDD severity over PBO paired with low-rCBF or SERT with high-rCBF, all $p<.05$. SERT given to those with high-rCBF in the parahippocampus and middle temporal gyrus resulted in better outcomes over PBO with high-rCBF, both $p<.03$. Number needed to treat to achieve remission on SERT for these regions were 2.64-7.25.
Conclusions: Perfusion moderators were identified in brain regions implicated in the etiology of MDD and its related circuitry, e.g. anhedonia and reward processing. These results highlight the potential role of using perfusion as clinical biomarker of treatment response.
Supported By: U01MH092221; U01MH092250
Keywords: Neuroimaging, Major Depressive Disorder (MDD), Cerebral Blood Flow, Prediction of Treatment Outcome, Biomarkers

S133. Resting State Bold Signal Variability Correlates With Clinical Dimensions in Euthymic Bipolar Patients

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Background: Resting-state (RS) functional magnetic resonance imaging (fMRI) is increasingly used in clinical populations to explore alterations in the organization of brain networks. In euthymic bipolar patients (BD), RS fMRI studies have shown inconclusive results, mainly because of the disparities in technics, but also due to the heterogeneity of the population. Here we use an approach that aims at linking clinical dimensions and BOLD signal variability in two datasets (Geneva and Paris).
Methods: BOLD signal variability was computed using the standard deviation of each voxel's signal across the time-course. We applied partial least-squares correlations (PLSC) in order to link voxel-wise BOLD variability and clinical measures in euthymic BD patients and healthy controls. PLSC is a multivariate data-driven statistical technique that aims to maximize the covariance between two modalities
Results: We found several significant brain-behavior correlations. Rumination tendency and depression were associated with increased variability in the ACC, vmPFC, but also the OFC, pallidum, cerebellum and brain stem (N=53 [23 patients and 30 controls]). On the other hand, increased affective instability, depression and mania correlated with less reactive occipital cortex, cerebellum, cingulate gyrus and other medial limbic regions in bipolar patients (N=34 patients).
Conclusions: Decreased variability of brain signal in limbic regions associated with increased level of affective lability, residual symptoms or severity of disease to different extents might represent a marker of non-efficient emotion regulation processes in bipolar patients. In both patients and controls, tendency to ruminate and depression correlates with increased variability not only in self-related regions but also subortical areas.
Supported By: FondaMental Suisse Foundation; Swiss National Fund; Synapsy NCCR
Keywords: Bipolar Disorder, Resting State fMRI, Clinical Features

S134. Neural Differences Between Euthymic Bipolar and Remitted Unipolar Depressed Individuals: An fMRI Study of Emotion Processing

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Background: Neural trait markers that differentiate bipolar and unipolar depression are critical to avoid misdiagnosis and improve clinical outcomes for individuals with bipolar disorders.

Amygdala response to emotion processing has been found to be a depression specific state marker in bipolar disorder. It is unknown if this neural substrate persists in euthymic/remitted states and potentially could be a trait marker for differentiating these disorders. This study investigated potential differences in amygdala activity and connectivity during emotion processing in euthymic/remitted bipolar (eBP) and unipolar depressed (rUD) populations.

Methods: 23 eBP and 25 rUD individuals matched for age, sex, number of depressive episodes and severity completed fMRI tasks measuring conscious and non-conscious emotion processing of threat (anger, fear, disgust), sad, happy and neutral faces. Amygdala activations and PPI functional connectivity were analyzed using SPM8 and compared between groups using cluster wise corrections (FDR$p<0.05$).

Results: Significant left amygdala hypoactivation for eBP relative to rUD was observed during conscious and non-conscious sad and neutral processing and for non-conscious happy faces. There was also increased left amygdala-insular connectivity for eBP (eBP>rUD) for conscious/non-conscious sad and conscious threat processing, while decreased left amygdala-medialOFC connectivity (eBP<rUD) for conscious/non-conscious happy faces was observed.

Conclusions: Amygdala activation and connectivity during facial emotion processing can differentiate euthymic bipolar disorder patients from remitted depressed patients. These findings suggest that fMRI brain measures can be used to identify trait-specific markers that in turn characterize and thus potentially distinguish bipolar and unipolar depression largely independent of illness state.

Supported By: National Health and Medical Research Council (NHMRC) of Australia

Keywords: Bipolar Disorder, Unipolar Major Depression, Functional MRI, Functional Connectivity, Emotional Processing

S135. Reduced Cerebrovascular Reactivity Among Adolescents With Bipolar Disorder

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Background: Cardiovascular disease (CVD) is excessive and premature among individuals with bipolar disorder (BD). Cerebrovascular reactivity (CVR), reflecting capacity of the brain's blood vessels to vasodilate when induced by vasoactive substances, is a marker of cerebrovascular health. Despite informative findings in other diseases, CVR has not previously been examined in BD.

Methods: CVR was measured using blood-oxygenation-level dependent (BOLD) functional magnetic resonance imaging (fMRI) at 3-Tesla analysed voxel-wise and regionally in the five major regions of the brain. Twenty-five adolescents with BD and 25 age and sex-matched psychiatrically healthy controls (HCs) completed six 15-second breath-holds (BHs). Body mass index (BMI) and pulse pressure were examined as vascular risk factors.

Results: In whole-brain analyses, BDs had lower CVR in the posterior cingulate gyrus and periventricular white matter. There was a significant main effect of BMI on CVR. When controlling for differences in BMI, additional between-group CVR differences were observed in the temporal poles, supramarginal gyrus, and lingual gyrus. There were no significant regions in which CVR was greater in BD vs. HC. CVR was not associated with mood symptoms.

Conclusions: The findings of this study provide preliminary evidence of cerebrovascular dysfunction in BD, including regions known to be susceptible to frank cerebrovascular dysfunction and/or disease. Future prospective studies addressing the association of CVR with mood symptoms, neurocognition, treatment effects, and cerebrovascular disease are warranted.

Supported By: Ontario Mental Health Foundation

Keywords: Bipolar Disorder, Cerebrovascular Reactivity, Adolescents, BOLD fMRI

S136. Gene Knockout of Caspase-1 Improves the Depressive-Like Behaviour via Increasing the Surface Expression of AMPArs

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Background: It is well known that the IL-1β converting enzyme caspase-1 is an inflammatory caspase, and activation of caspase-1 involves the response of immune cells to both pathogen-derived and endogenous mediators by the formation of inflammasome complexes. In addition to its role in peripheral inflammation, growing evidences also indicate that caspase-1 mediated neuroinflammation in the brain mediates depression-like behavior induced by LPS or chronic stress. However, how the increased caspase-1 in the brain influences the depressive-like behavior remains largely unknown.

Methods: To address this issue, we examined the effects and underlying mechanisms of caspase-1 on preclinical murine models of depression.

Results: We found that loss of caspase-1 expression in caspase-1 knockout mice alleviated chronic stress-induced depression-like behaviors, whereas overexpression of

caspase-1 in the hippocampus of wild-type mice was sufficient to induce depression-like behaviors. Chronic social defeat stress (CSDS) reduced glutamatergic neurotransmission and decreased surface expression of AMPA receptors in hippocampal neurons of WT mice, but not caspase-1 knockout mice. Importantly, pharmacological inhibition of caspase-1 signaling pathway prevented the depression-like behaviors and the decrease in surface expression of AMPARs in stressed WT mice. CSDS-induced depression-like behaviors can be mimicked by exogenous intracerebroventricular administration of IL-1beta in both WT and caspase-1 knockout mice.
Conclusions: Our findings demonstrate that an increase in the caspase-1 facilitates AMPAR internalization in the hippocampus, which dysregulates glutamatergic synaptic transmission, eventually resulting in depression-like behaviors.
Funding Source: NSFC
Keywords: Depression, caspase-1, AMPA Receptor

S137. Gray Matter Volumes in Major Depression and Suicidal Behavior

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Background: Structural brain deficits is linked to risk for suicidal behavior although findings are inconsistent to-date. This may be due to the heterogeneity of suicidal behavior, including variation in suicidal intent and lethality of the suicidal act. We hypothesized that depressed higher-lethality suicide attempters, who may more closely resemble suicide decedents, would have smaller prefrontal cortical (PFC) volume compared to depressed non-attempters.
Methods: Structural T1 magnetic resonance imaging scans were collected on 77 individuals with major depressive disorder; 11 of whom had a history of higher-lethality suicide attempts scoring three or more (at minimum, mild physical injury requiring medical intervention) on the Beck Scale for Medical Damage, and 66 of whom were non-attempters. Voxel-based morphometry analysis was performed to examine differences in gray matter volume (GMV) between the two groups using brain-wide and region-of-interest (ROI) approaches, controlling for age, sex and total intracranial volume. The relationship between GMV and current depression severity, and life-time impulsiveness, aggression and cognitive control were examined.
Results: Both brain-wide and ROI analyses showed that higher-lethality suicide attempters have greater GMV in dorsolateral PFC, orbitofrontal cortex and insula compared to non-attempters. No correlations were detected between clinical variables and GMV.
Conclusions: Our hypothesis was not supported. Previous studies found that some higher-lethality suicide attempters have enhanced planning, response inhibition and delayed reward capabilities. Our findings are therefore consistent with a model in which PFC and insula gray matter volumes mediate enhanced executive control impacting suicide attempt lethality. Future studies are needed to explicitly evaluate this model in a prospective manner.
Supported By: P50 MH090964; P50 MH062185; R01 MH040695; R01 MH093637; K08 MH079033; K08 MH085061
Keywords: Major Depressive Disorder (MDD), Suicide Attempts, Voxel Based Morphometry, Gray Matter Volume

S138. White Matter Integrity Predicts Anti-Depressant Response in Late-Life Depression

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Background: White matter integrity in fronto-limbic-striatal circuits are frequently reduced in depression. We investigated the effect of local tract integrity on antidepressant outcome in geriatric depression. Regions of interest (ROIs) comprised the callosal genu (GCC), anterior and posterior internal capsule (ALIC, PLIC), cingulum (CGC), inferior and superior fronto-occipital and superior longitudinal fasciculi (IFO, SFO, SLF).
Methods: Twenty-six patients (mean age=70.5, SD=7.4; 15 female; Hamilton Depression Rating Scale, HAM-D>=16) underwent diffusion-weighted imaging and a 12-week escitalopram trial. Baseline fractional anisotropy (FA), axial, radial and mean diffusivity (AD, RD and MD respectively) were derived using FSL's Tract-Based Spatial Statistics (TBSS) and the ICBM-DTI-81 white matter atlas. Symptoms were re-assessed post-treatment. A general linear model assessed the effect of baseline diffusion metrics on HAM-D change, controlling for age, sex and baseline HAM-D.
Results: Fifteen patients achieved remission (HAM-D<=7). FDR-corrected significant negative correlations were found between FA and HAM-D change for ALIC (r=-.53, p=.007), PLIC (r=-.45, p=.02), IFO (r=-.43, p=.03), SFO (r=-.43, p=.03), SLF (r=-.46, p=.02) and CGC (r=-.40, p=.05), but not for GCC (r=-.18, p=.4.). Follow-up analysis revealed positive correlations between RD and HAM-D change in ALIC, CGC, IFO, PLIC and SLF. MD correlated positively with CGC and SLF. AD was not significantly correlated.
Conclusions: Higher pre-treatment white matter integrity in tracts implicated in depression predicted greater symptom improvement after anti-depressant treatment in late-life depression. Regional demyelination and axonal degeneration suggest poor treatment outcome. White matter integrity may serve as a relevant predictor for treatment outcomes in geriatric depression.
Supported By: R-01 MH097892
Keywords: Brain Imaging, Geriatric Depression, White Matter Integrity, Antidepressant Response

S139. Accelerated Cortical Thinning Within Structural Brain Networks is Associated With Irritability in Youth

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Background: Irritability is an important dimension of psychopathology that spans multiple clinical diagnostic categories, yet its relationship to abnormal patterns of brain development remains sparsely explored. Here, we examined how trans-diagnostic symptoms of irritability relate to the development of structural brain networks.
Methods: All participants (n=118, 74 females) completed structural brain imaging with 3 Tesla MRI at two time-points (mean age at T2: 20.9 years, mean inter-scan interval: 5 years). Irritability was assessed using the Affective Reactivity Index, and cortical thickness was quantified using ANTs. Structural covariance networks were delineated using Non-negative Matrix Factorization, an advanced multivariate analysis technique. Both cross-sectional and longitudinal associations between irritability at T2 and thickness within each network were evaluated using generalized additive models with penalized splines. The False Discovery Rate ($q<0.05$) was used to correct for multiple comparisons.
Results: NMF identified 18 structural covariance networks. Cross-sectional analysis at T2 revealed that 12 of these networks were associated with irritability, with higher levels of irritability being generally associated with thinner cortex. Effects were particularly prominent in regions of the default-mode network, including the posterior cingulate, ventromedial prefrontal, lateral temporal, and medial temporal cortex (all q's<0.003). Longitudinal analyses revealed significantly accelerated cortical thinning in 8 of these networks.
Conclusions: These findings suggest that irritability in youth is associated with accelerated cortical thinning, particularly within elements of the default mode network. Aberrant maturation of regions within the default mode network important for affect regulation may in part underlie symptoms of irritability in youth.
Supported By: RO1
Keywords: Longitudinal Brain Imaging, Developmental Psychopathology, Irritability, Structural Magnetic Resonance Imaging, Dimensional

S140. Brain-Derived Neurotrophic Factor (BDNF) as a Potential Biomarker for Resting-State Network Remodeling After Ketamine Infusion

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Background: Ketamine is a fast-acting antidepressant with maximum efficacy at 24h [Zarate(2006)]. Patients with depression show hyperconnectivity within Default Mode Network (DMN) [Kaiser(2015)] and lower blood level of Brain-derived neurotrophic factor (BDNF) [Haile(2013)]. BDNF is an activity-dependent modulator of neurogenesis [Brigadski(2014)]. Ketamine may induce its effects through an improved neuroplasticity via BDNF-signaling and large-scale network remodeling [Duman(2012), Scheidegger(2012)]. Aim: Explore the interrelation between ketamine-induced peripheral BDNF change and network reconfiguration in DMN and investigate its temporal specificity.
Methods: In this double-blind and randomized study, healthy subjects received an intravenous infusion of either ketamine (0.5 mg/kg, n=31) or saline (n=30). Resting-state fMRI scans and BDNF plasma levels were acquired at baseline, 1h, and 24h. Functional Connectivity (FC) maps were calculated for a DMN seed (dorsal posterior cingulate, dPCC). Mean FC values were extracted and correlated with BDNF level. Furthermore, whole-brain regression analysis was done with BDNF as regressor.
Results: Decreased FC between dPCC and dorsomedial prefrontal cortex (dmPFC) was observed 24h post-infusion ($p<0.05$FWE). Rpm-ANOVA showed significant time*treatment interaction in BDNF between both groups ($p<0.05$). Post hoc tests showed an BDNF increase in ketamine group compared to placebo group at 1h and 24h ($p<0.05$). Larger BDNF increase at 1h and 24h correlated significantly with stronger FC disconnection between dPCC and dmPFC ($p<0.05$, Bonferroni corrected). Regression analysis showed multiple cortical structures within and outside the DMN which were associated with BDNF increase after 24h.
Conclusions: BDNF, as a modulator of neuroplasticity, is associated with strong within and between network reconfigurations of DMN after a single ketamine infusion.
Supported By: German Research Foundation (SFB and DFG), Centre for Behavioural and Brain Sciences, and Leibniz Association, Germany. M. Woelfer is supported by a stipend of the Medical Faculty of University of Magdeburg, Germany and German Academic Exchange Service.
Keywords: Ketamine, Resting State fMRI, BDNF, Antidepressant, Default Mode Network

S141. Electroconvulsive Therapy Leads to Plastic Changes in the Medial Forebrain Bundle Associated With Improvement in Anhedonia and Depression Severity

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Background: Electroconvulsive therapy (ECT) is the most effective treatment for Major Depressive Disorder (MDD).

Despite its clinical effectiveness, the mechanism of action of ECT remains unclear. In this study, we used diffusion tensor imaging (DTI) to evaluate the effects of ECT in the medial forebrain bundle (MFB), a prominent fiber pathway of the mesocorticolimbic system. We hypothesize that ECT would lead to variations in DTI measures in the MFB, which would correlate with a decrease in depression severity (syndromal efficacy) and anhedonia (dimensional).
Methods: DTI data were acquired in 11 patients with MDD who underwent treatment with ECT. Depression severity was assessed with the Quick Inventory of Depressive Symptoms (QUIDS) and anhedonia with the Snaith Hamilton Pleasure Scale (SHAPS). The MFB was extracted using multi-tensor tractography. We compared fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and trace diffusivity indices before and after ECT. We also evaluated the associations between changes in DTI measures and clinical response.
Results: Analysis revealed that ECT lead to a significant decrease in AD in the right MFB ($t=2.81$, $P=0.018$). We observed a significant association between greater AD decrease and improvement in depression severity ($r=0.66$, $P=0.02$), and anhedonia levels ($r=0.69$, $P=0.018$).
Conclusions: ECT is associated with white matter neuroplastic changes in the MFB that explain the syndromal (categorical) response, as well as dimensional improvement in reward processing (anhedonia). Our results suggest that therapeutic response after ECT is achieved through the modulation of pathological networks involved in mood regulation, particularly positive affect and reward pathways.
Supported By: NIH R01 MH112737-01
Keywords: Major Depressive Disorder, Electroconvulsive Therapy, Reward Circuitry, Diffusion MRI

S142. A Predictive Approach to Identify Clinical State, Emotional Valence and Pharmacologic Effect in Human Task-Based fMRI Data

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Background: Clinically approved antidepressants modulate the brain's emotional valence circuits, suggesting that the response of these circuits could serve as a biomarker for screening candidate antidepressant drugs. Here, we apply a cross-validated predictive model to classify clinical state, emotional valence, and pharmacologic effect across eight task-based fMRI studies ($n=306$) of the effect of antidepressant administration on emotional face processing.
Methods: Subject-level contrast of parameter estimates were created using FSL FEAT. Whole-brain parcellation schemes were brought into subject space and used as a feature-reduction step. Each parcel was used as a feature within a gradient-boosting machine algorithm to classify: 1) clinical state (healthy vs unhealthy subjects across subjects); 2) emotional valence (fearful vs happy face visual conditions within and across studies); 3) pharmacologic effect (drug vs placebo administration within and across studies). Leave-one-out cross validation was used for all across-subject classifications; leave-one-study-out was used for across-study classifications. Feature weightings were mapped back into MNI-152 space.
Results: We found consistent patterns of brain activity that classify clinical state (70% accuracy), emotional valence (70% across-subjects; range from 50-87% across-study), and pharmacologic effect (50-84%) across 306 subjects. Subject population (healthy or unhealthy), treatment group (drug or placebo), and drug administration protocol (dose and duration) affected this accuracy with similar populations better predicting one another.
Conclusions: Consistent functional patterns across studies suggests that this line of investigation is useful for biomarker development in mental health and in pharmacotherapy development. It also suggests that case-controlled designs and more standardized protocols could increase the yield of the drug development pipeline.
Supported By: Yale School of Medicine Research Funding
Keywords: BOLD fMRI, Pharmacotherapy, Antidepressant, Mood Disorder

S143. Steroid Hormone Analysis of Retrospective Maternal Hair and Newborn Nail Samples Indicate Effects of Prenatal Stress on Postpartum Well-being of Mother and Offspring

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Background: Distress by life events in pregnancy may have a critical impact on maternal postpartum mental health, pregnancy outcomes and off-spring's development. As exposure to stress steroids could be assessed retrospectively in maternal hair and newborn nail samples, the aim of this study was to examine, if such assessments could predict prenatal stress effects on mother's and off-spring's well-being.
Methods: In a prospective cohort of 79 healthy, timely delivering mothers (age: 32.8 ± 4.5) distress during pregnancy, postpartum depression and infant irritability at 3 months p.p. were assessed with questionnaires. In maternal hair samples corresponding to the 3rd trimester and in off-spring nail clips of prenatal origin a panel of steroid hormones was analyzed with mass spectroscopy, respectively.
Results: In mothers, late pregnancy stress was associated with decreased hair cortisone and an increased hair cortisol/cortisone ratio ($p<.05$, resp.), and with increased depression scores at 3 months p.p. ($p<.02$); and hair steroid levels predicted depression scores ($r=-.25^*$, $r=.52^{**}$, resp.). In off-springs, pregnancy stress in 1st trimester was related to increased DHEA i.n. and increased irritability at 3 months p.p. ($p<.05$, resp.), and DHEA predicted irritability ($r=.52^{**}$). By contrast, an increased maternal hair cortisol/cortisone ratio reflecting stress exposure at 3rd trimester was related to

increased fetal cortisol i.n. (r=.43*) which predicted decreased birth weight (r=-.30*).
Conclusions: Retrospective means of analysis of maternal hair and fetal nail steroids are useful to indicate effects of pregnancy stress on mother and off-spring. Our results confirm the hypothesis of fetal programming by stress exposure in early pregnancy.
Supported By: Gottfried and Julia Bangerter-Rhyner-Foundation, Berne, Switzerland; Forschungsförderungsfond der Universitären Psychiatrischen Kliniken Basel, Switzerland
Keywords: Corticosteroid Stress Hormones, Hair Cortisol, Postpartum Depression, Fetal Programming, Pregnancy

S144. Convergent Relationships Between Inflammatory Cytokines, Childhood Adversity, and Neuropsychological Function in Adolescents With Depression

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Background: Inflammatory cytokines are implicated in early life adversity (ELA), depression, and impairment in executive function and memory in adults. Whether these links are present during adolescence, a critical period of brain development and when vulnerability to ELA and depression is heightened, is not fully understood.
Methods: Serum levels of interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha (TNF-α) were measured in 71 un-medicated adolescents aged 12-17, including forty with any mood disorder (AMD) and 31 healthy controls (HCs). ELA was determined based on moderate or high scores on the Childhood Trauma Questionnaire subscales. Adolescents completed a neuropsychological assessment battery and the Children's Depression Rating Scale, which were factor-analyzed into dimensions of neuropsychological function and depression.
Results: IL-6 elevations in AMD participants with (n=22) and without ELA (n=18) relative to HCs (p=.021) were related to a depressed mood factor (β=.97, p=.045). TNF-α elevations in AMD without ELA (p=.045) were related to increased somatic symptoms (β=1.91, p=.013). Across all participants, inflammation was associated with poorer verbal learning (IL-1β; β=-1.12, p=.016) and visual learning/memory (IL-6; β=-2.09, p=.030). ELA was associated with poorer psychomotor speed (p=.023), interference resolution (p=.021), inhibitory control (p=.050), and verbal learning (p=.035). An interaction between diagnostic group, ELA, and IL-1β, significantly contributed in predicting inhibitory control (β=2.20, p=.048).
Conclusions: Inflammation alone was associated with depressed mood and memory dysfunction in adolescents, whereas inflammation may interact in at-risk, depressed and trauma-exposed youth, to predict somatic complaints and executive dysfunction. Inflammation probes may contribute to early identification of risk for depression and neuropsychological dysfunction.
Supported By: NIMH R01 MH098554 (GNP) & F31 MH108258 (ATP)
Keywords: Inflammation, Adolescent Depression, Executive Function, Memory

S145. Effects of an Acute Bout of Exercise on Reward Functioning

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Background: Exercise has been proposed as a treatment for several psychiatric disorders. Exercise may act in part through beneficial effects on reward functioning, as it alters neurotransmitter levels in reward-related circuits. However, there has been little investigation of the effect of exercise on reward functions in humans. We hypothesized an acute bout of exercise would increase motivation for and pleasurable responses to rewards in healthy humans. In addition, we examined possible moderators of exercise's effects, including demographics, general fitness and previous exercise experience.
Methods: 35 healthy adults completed exercise and sedentary control sessions in randomized, counterbalanced order. At the exercise session, participants ran at 5% above their individually-determined lactate threshold for 20 minutes. At the control session, participants sat quietly for 20 minutes. Immediately after each activity, participants completed measures of motivation for and pleasurable responses to rewards.
Results: Exercise did not increase motivation for or pleasurable responses to rewards on average. However, there was a significant moderating effect of years running ($F[1, 32] = 4.30$, $p = 0.05$, $\eta 2 = 0.12$), such that individuals who had been runners for more years showed increased motivation for rewards after exercise, while individuals with less years running showed decreases. General fitness did not have a similar moderating effect.
Conclusions: Acute exercise improved reward functioning only in individuals accustomed to that type of exercise. This suggests a possible conditioned effect of exercise on reward functioning. Previous experience with the exercise used should be examined as a possible moderator in exercise treatment trials.
Keywords: Exercise Intervention, Positive Emotion, Reward Responsiveness

S146. Volumetric Changes in the Right Hippocampus and Dentate Gyrus Explain Dimensional Improvement in Negative (but not Positive) Affect After ECT

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Background: Electroconvulsive Therapy (ECT) is the most effective treatment in psychiatry, and among the most effective in medicine. While a number of studies have described right hippocampal volume increases, the relationship of these

changes with clinical response remain unclear. We study these dynamics by quantifying dentate gyrus volumes beyond the hippocampus (subfield anatomy), and positive vs. negative affect beyond overall depression severity (dimensional assessments).
Methods: We studied 16 patients treated with ECT for depression. Before and after acute treatment, we obtained high-resolution T1-weighted MRI scans, measures of clinical depression severity (QIDS-SR), and of positive and negative affective dimensions (PANAS). We used FreeSurfer 6.0 for structural reconstruction and segmentation of images (hippocampal module for subfield segmentation). Significance levels were set at $p<0.05$ after family-wise error correction for multiple comparisons.
Results: ECT led to right but not left hippocampal volume increase, and we observed this in the dentate gyrus volume. These changes did not explain the syndromal clinical improvement of depression as measured by the QUIDS-SR (categorical). Nevertheless, we identified a significant relationship between right hippocampal volume change and improvement of negative (but not positive) affective dimensions ($p=0.015$). This relationship also existed with the dentatte gyrus ($p= 0.002$).
Conclusions: These results confirm ECT-mediated right hippocampal volume increase, and report a parallel increase in dentate gyrus volume. These volumetric changes do not explain changes in overall depression severity. More nuanced relationships between volume change and improvement in affective dimensions may pave the way for a dimensional explanation of ECT effects.
Supported By: R01 MH112737-01 (PI Camprodon)
Keywords: Electroconvulsive Therapy (ECT), Mood Disorders, Neuromodulation, Brain Magnetic Resonance Imaging (MRI), Hippocampus

S147. Resting-State EEG Source Analysis in Depressed Patients Treated With Electroconvulsive Therapy and Magnetic Seizure Therapy

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Background: Electroconvulsive therapy (ECT) and magnetic seizure therapy (MST) are highly effective treatment strategies for patients with severe depression. Presently, the mechanisms of action for ECT and MST are unclear. In this study, we investigate spectral activity and functional connectivity changes in predefined neural circuits associated with depression using resting-state electroencephalogram (EEG).
Methods: Patients were participants in a double blind, randomized controlled trial that contrasted the efficacy and side effects of ECT and MST. We included 10 patients (age 48.6 $\pm$ 9.2, 6 males, 7 ECT) for resting EEG analysis. EEG preprocessing was conducted using MATLAB EEGLAB toolbox. Reconstruction of the electrical activity of the brain in a 3D model and estimation of functional localization and connectivity were performed using Low-Resolution Electromagnetic Tomography (LORETA). We performed network parcellation using the Harvard-Oxford Atlas (HOA) and Broadman areas.
Results: In the eyes open condition, there was increased theta connectivity between left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) in responders compared to non-responders ($p < .001$). A similar increase was detected between right DLPFC and orbitofrontal cortex (OFC) ($p < .001$). In the eyes closed condition, we found decreased gamma power in the middle frontal gyrus for responders ($p < .05$).
Conclusions: Results suggest DLPFC, ACC and OFC regions are involved in the mechanism of action for ECT and MST. Changes in theta and gamma power may be an indicator of treatment response, or could be associated with cognitive impairments after treatment.
Supported By: Stanley Research Foundation; and NIH Intramural Research Program
Keywords: Depression, Electroconvulsive Therapy (ECT), Magnetic Seizure Therapy, Electroencephalography (EEG), Functional Connectivity

S148. Effects of Low Field Magnetic Stimulation in Depression and Structural Brain Connectivity

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Background: Recently, there has been some interest in the mood-enhancing effects in individuals suffering from depression using Low Field Magnetic Stimulation (LFMS). The effects of LFMS on the brain are not well understood; this study uses network analysis to investigate the effects of this treatment on major depression.
Methods: 57 individuals with a diagnosis of unipolar depression (baseline Hamilton Depression Rating Scale-24, HAMD24, 27.1+/-5.9) consented to participate in a double-blind, sham-controlled study, in which three 20-minute sessions of LFMS were administered. Global tractography was performed using MRtrix3 from diffusion tensor imaging data that was collected before and after treatment. A connectivity matrix using 471 brain regions based on the Harvard-Oxford Atlas was generated. Nodal strength, betweenness centrality, clustering coefficient, and local efficiency were computed.
Results: Baseline betweenness centrality correlated with change in HAMD before and after treatment at the left middle frontal gyrus ($t=2.9$, $p<.01$), right frontal pole ($t=-3.5$, $p<.01$), and left parahippocampal gyrus ($t=-2.9$, $p<.01$). The change in betweenness centrality before and after the treatment correlated with the change in HAMD at the right frontal pole ($t=3.0$, $p<.01$) and left parahippocampal gyrus ($t=2.8$, $p<.01$). Baseline nodal strength also correlated with the change in HAMD at left superior temporal gyrus ($t=3.0$, $p <.01$). The other graph theory metrics were not significant.
Conclusions: Graph theory measures such as betweenness centrality and nodal strength can be used to predict LFMS treatment response. Changes in the middle frontal gyrus, frontal pole, parahippocampal gyrus, and superior temporal

gyrus are potentially important for understanding antidepressant mechanisms.
Supported By: This work was supported in part by Tal Medical and the NIH Intramural Research Program
Keywords: Diffusion Tensor Imaging (DTI), Graph Theory, Depression, Low Field Magnetic Stimulation

S149. Randomized Double-Blind Study of Long Pulse Width vs. High Intensity Subcallosal Cingulate Stimulation for Treatment-Resistant Depression

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Background: Subcallosal cingulate (SCC) deep brain stimulation (DBS) is an investigational treatment for treatment-resistant depression (TRD). Stimulation adjustment is required to optimize the clinical outcome, but controlled data on optimal stimulation parameters is limited. We examined the efficacy and safety of long pulse width (LPW) vs High intensity (HI) stimulation.
Methods: Twenty-two patients (12M: 11F, age range 23-69) with TRD received bilateral DBS implants in the SCC. They were randomized to receive either LPW (4V, 210-450 us) or HI (90 us, 4-8 V) stimulation in the first 6 months. Either PW or V was increased monthly if the response was inadequate ($< 20\%$ improvement in HDRS from the previous evaluation) in the respective groups. Non-responders were crossed over to the other stimulation mode for another 6 months. Primary outcome measure was change in Hamilton Depression Rating Scale 17 (HDRS) at 6 and 12 months and 50% reduction from baseline was considered as response.
Results: Both groups showed significant improvement in HDRS scores at 6 months ($p < 0.001$), with no difference between groups in symptom scores ($p = 0.61$) or response rates (LPW-50%; HI-45%). Similarly, there were no differences in HDRS scores between cross over groups at 12 months. Overall, the response rate going from HI to LPW was 40% and LPW to HI was 25%. Adverse effects were mild and comparable between groups.
Conclusions: In this small study both LPW and HI stimulation was equally effective for TRD symptoms. LPW stimulation may have a role in optimizing SCC-DBS.
Supported By: Alberta innovates and health solutions (AIHS)
Keywords: Deep Brain Stimulation, Subcallosal Cingulate, Treatment Resistant Depression, Long Pulse Width Stimulation, High Voltage Stimulation

S150. Inhibitory Neurotransmission Predicts TMS-Related Functional Connectivity in Depressed Individuals

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Background: High-frequency repetitive transcranial magnetic stimulation (rTMS) targeted to the left dorsolateral prefrontal cortex (DLPFC) in depression has been associated with changes in both γ-aminobutyric acid (GABA) levels and resting state functional connectivity. The current project examines whether functional connectivity following open-label TMS is related to pre-post changes in GABA levels.
Methods: 26 individuals diagnosed with a current depressive episode underwent a 5-week open-label treatment with 10Hz rTMS targeting the left DLPFC. GABA levels in the medial prefrontal cortex were measured using proton magnetic resonance spectroscopy (MRS) pre- and post- treatment. Resting state functional connectivity was also obtained before and after rTMS. Both MRS and fMRI were obtained using a 3.0T GE Scanner.
Results: Preliminary analyses revealed that the change in GABA levels was: a) negatively correlated with resting state functional connectivity within the default-mode network; b) positively correlated with connectivity between the default mode network and the frontoparietal (task-positive) network; and c) negatively correlated with connectivity within the frontoparietal network. These patterns appear to be responder-specific.
Conclusions: TMS-related changes in resting state functional connectivity appear to be related to GABA levels in the medial prefrontal cortex. These data raise the possibility that changes in inhibitory neurotransmission may play a mechanistic role in rTMS-driven normalization of functional connectivity.
Supported By: This work was supported by grants from the Brain and Behavior Research Foundation (National Alliance for Research on Schizophrenia and Depression Young Investigator Award) and Neuronetics, Inc., awarded to Marc Dubin and by funds from the Department of Psychiatry at Weill Cornell Medical College. CL
Keywords: HF-rTMS, Depression, Resting State Functional Connectivity, GABA

S151. Deep Brain Stimulation of the Medial Forebrain Bundle in Treatment-Resistant Depression- Criteria for Patient Selection

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Background: Antidepressant efficacy has been demonstrated in about 70% of patients suffering from treatment-resistant depression (TRD) treated with deep brain stimulation of the medial forebrain bundle (slMFB). We analyzed possible predictors of response to slMFB-DBS as well as characteristics of non-response or dropout.
Methods: Twenty-four TRD patients were treated with DBS to the slMFB. Typical predictors of response (demographic: gender; clinical: ECT-response, age at depression onset, time since diagnosis, score in depression rating scales, clinical

subtype, unipolar vs. bipolar, treatment resistance; personality: NEO-FFI, affective neuroscientific personality scale, ANPS) were assessed with student's t-test or X2 Test and with Spearmen's correlation coefficient. Non-responders/dropouts were analyzed with descriptive methods.
Results: Strong responders did not differ in demographic or clinical characteristics from week responders. Response was not correlated with variables of severity, chronicity or treatment resistance but with a reduced CARE dimension (ANPS) (r=-0.643, p= 0.007). Nonresponse/dropout was associated with intracranial bleeding (n=1); methylphenidate abuse (n=2), acute social stressors (n=1), narcissistic personality disorder (n=1).
Conclusions: A high percentage of responders was found in this study. Typical predictors of response did not explain response status because this sample was highly selected and homogeneous. All patients were severely, chronically depressed and very treatment-resistant. Patients with melancholic or atypical depression, suffering from unipolar or bipolar disorder had a similar high chance of response to slMFB-DBS. Comorbidities (e.g. personality disorder, addiction) could be relevant factors in future studies but were excluded.
Supported By: Dr. Schlaepfer and Dr. Coenen obtained a grant from Medtronic Inc.
Keywords: Deep Brain Stimulation, Treatment-Resistant Depression, Medial Forebrain Bundle, Predictors of Response, Personality

S152. Stimulating Young Minds: Investigating a Next Generation Treatment for Depression in Youth

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Background: One third of young depressed patients do not respond to antidepressants and are at risk for chronic treatment resistance. Repetitive transcranial magnetic stimulation (rTMS) is efficacious in treating depression, however, few studies have investigated patients at earlier stages of illness when providing optimal treatments are likely to result in better response outcomes. A subset of patients show inadequate response to rTMS and identifying features of patients that predict response is needed to inform personalised approaches.
Methods: In this open-label study, 17 young inpatients and outpatients with depression (aged 18-30; 22±3.8) were recruited. Neuronavigationally targeted high frequency (10 Hz) rTMS was administered at 110% of resting motor threshold on the left DLPFC for 45 trains of 4 seconds for 20 sessions over 4 weeks. Clinical interview, cognitive assessment and, psychosocial self-report scales were carried out within 2 weeks pre- and post-treatment.
Results: Paired-samples t-tests revealed that depression, anxiety and psychiatric symptoms were significantly reduced with rTMS treatment (all p<.05) but no significant changes in cognitive or psychosocial functioning were found (p>.05). Greater improvements in depressive symptoms were associated with better pre-treatment set-shifting performance (p<.05; r=.53). In patients with moderate-severe depression (n=9), greater improvements in psychiatric symptoms were associated with later age of illness onset (p<.05; r=.88).
Conclusions: In keeping with the literature, rTMS improves depressive, anxiety and psychiatric symptoms in young people. These data suggest that cognition may have utility in predicting rTMS treatment response and targeting rTMS earlier in the course of illness may result in better response outcomes in young people with depression.
Supported By: Society for Mental Health Research (Aus), National Health and Medical Research Council (Aus)
Keywords: Youth, Depression, Repetitive Transcranial Magnetic Stimulation

S153. Cognitive Effects of Transcranial Direct Current Stimulation Treatment in Patients With Major Depressive Disorder: An Individual Patient Data Meta-Analysis of Randomised Sham Controlled Trials

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Background: Transcranial direct current stimulation (tDCS) has emerged as a promising new treatment for major depression. While recent randomised sham controlled studies found tDCS to have antidepressant effects, it remains to be determined whether a tDCS treatment course may also enhance cognitive function independent of mood effects in depressed patients.
Methods: This systematic review and individual patient data (IPD) meta-analysis examined cognitive outcomes from randomised sham controlled trials of tDCS treatment for major depression. Cognitive outcomes were examined for 12 outcomes, which covered key cognitive domains of global cognitive functioning, verbal memory, executive functioning, attention and working memory. Subgroup analyses examined whether tDCS effects on cognitive function differed according to certain patient level characteristics.

Seven randomised sham controlled trials (n=478 participants, 260 in active and 218 in sham) of tDCS for major depression (unipolar and bipolar) were included in the analysis.
Results: Quality assessments showed that the risk of bias was low. Results showed no cognitive enhancement after active tDCS compared to sham for the 12 cognitive function outcomes investigated. Active relative to sham tDCS treatment was associated with reduced performance gains on a measure of processing speed (β= -0.33, 95% CI -0.58; -0.08, p=0.011). This effect was greater in participants who were female, had

unipolar depression, or had higher pretreatment global cognitive functioning.
Conclusions: Active tDCS treatment for depression did not show cognitive benefits independent of mood effects. Rather, tDCS treatment relative to sham stimulation for major depression may instead be associated with a reduction in processing speed gains.
Keywords: Transcranial Direct Current Stimulation (tDCS), Treatment, Major Depression, Bipolar, Cognition

S154. Deep Brain Stimulation in Depression Alters Amygdala Connectivity During Rest

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Background: Deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) is a promising treatment for patients with refractory depression. The amygdala is a key brain structure in the pathophysiology of depression. Here, we tested whether DBS affects functional connectivity of the amygdala using resting-state functional magnetic resonance imaging (FMRI).
Methods: 16 patients with treatment-resistant depression received DBS for one year before they underwent a randomised crossover phase, during which DBS was switched on or off for 2-4 weeks. Resting-state scans for both sessions were available for 11 patients. Data were analyzed using spm12, including standard preprocessing, bandpass filtering, and nuisance regression. Timeseries from the amygdalae were extracted and correlated with the rest of the brain. Significant clusters surviving a family wise error rate of 0.05 with a cluster defining threshold of 0.001 were reported.
Results: DBS on decreased amygdala connectivity with the precuneus (MNI: 10, -62, 30; p= 0.0005). Whereas the amygdala and precuneus were positively coupled during DBS off, amygdala-precuneus connectivity was negative during DBS on.
Conclusions: DBS treatment in patients with depression reverses functional connectivity between the amygdala and precuneus. The precuneus is a hub of the default mode network and is involved in self reflections and autobiographical memory, suggesting that DBS may limit the influence of the amygdala on self-reflective processes.
Supported By: ZonMw; Medtronic
Keywords: Deep Brain Stimulation, Depression, Resting State fMRI

S155. The Effect of Previous ECT Treatment on Responsiveness of MDD Patients to rTMS

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Background: Patients with major depressive disorder (MDD) who receive ECT and subsequently relapse often seek TMS as a less-invasive treatment option. Data are lacking regarding the effect of previous ECT on responsiveness to TMS treatment.
Methods: Data from n=235 MDD patients treated with rTMS at our TMS Clinic were retrospectively analyzed. IDS-SR and PHQ-9 depression scales were administered at the start and end of treatment. Baseline features and rTMS outcomes (response, remission, percent change) were compared for groups based on past history of ECT or none. Linear regression models examined predictors of positive outcome.
Results: There were no significant group differences in age, gender, treatment number, or duration of treatment course. Significantly more +ECT patients had past psychiatric hospitalization (94% vs. 53%, $p<0.001$) and there were trends toward higher depression severity at baseline for +ECT group (IDS-SR p=0.065; PHQ-9 p=0.055).

No significant group differences were found in post-treatment scores or in %change on either scale. Response (38% vs. 49% p=0.09) and remission (18% vs. 28%; p=0.06) rates tended to be lower for +ECT patients using IDSSR but not PHQ-9. When all variables (ECT, age, gender, past hospitalization, baseline scores, number treatments, number of weeks) were entered in regression models, ECT did not significantly predict responder or remitter status. Fewer number of sessions (p=.003) and more treatment weeks (p=.027) predicted better outcomes for +ECT patients.
Conclusions: Patients with past ECT were more depressed and had (trend-level) lower response rates, but in general, ECT history does not significantly predict rTMS outcome.
Supported By: R25MH101076
Keywords: ECT, TMS, MDD

S156. Cognitive Effects of Deep Transcranial Magnetic Stimulation for Late-Life Depression

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Background: Late-life depression (LLD) is a growing global public health issue due to demographic changes. LLD is associated with cognitive functioning impairment. Deep repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for depression in younger adults associated with improved cognition; however, the impact of deep rTMS on cognition in LLD has not been explored.
Methods: We randomized adults 60-85 years (n=52) with major depressive disorder (MDD) to sham or active deep rTMS (H1 coil, 6012 pulses, 18Hz, 120% resting motor threshold) delivered over the dorsolateral and ventrolateral prefrontal

cortex five days per week over four weeks. Cognitive outcomes were the Repeatable Battery for the Assessment of the Neuropsychological Status (RBANS) and two Delis-Kaplan Executive Function System (DKEFS) subscales: Color Word Interference (DKEFS-CWI) and Trail Making Test (DKEFS-TMT). The analysis used a linear mixed effects model for repeated measures and the primary outcome was group x time interaction.

Results: Active rTMS was superior to sham at achieving remission. The effect of time did not differ between active and sham deep rTMS for cognitive outcomes. We found a significant effect of time for: total RBANS ($F=37.1$;d.f.$=44.6$;$p<0.001$); RBANS subscales immediate memory ($F=12.5$;d.f.$=45.1$; $p<0.001$), delayed memory ($F=45.8$; d.f.$=45.1$;$p<0.001$), language ($F=9.6$;d.f.$=47.3$;$p=0.003$); and DKEFS-CWI (inhibition condition) ($F=9.5$;d.f.$=45.7$;$p=0.003$). All changes represented improvements from baseline.

Conclusions: There was non-specific improvement in cognitive functioning in LLD with both sham and active deep rTMS. Despite improvement in depressive symptoms, active deep rTMS was not associated with improved cognitive functioning compared to sham. Further analysis of cognitive changes in remitters compared to non-remitters is warranted.

Supported By: This study was supported by a Canadian Institute for Health Research University-Industry Sponsored Operating Grant in conjunction with Brainsway Ltd.

Keywords: Repetitive Transcranial Magnetic Stimulation, Cognitive Dysfunction, Geriatric Depression

S157. Neurocognitive Performance Predicts Treatment Outcome With Cognitive Behavioral Therapy for Major Depressive Disorder

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Background: Cognitive behavioral therapy (CBT) is an effective, widely-used treatment for depression, but predictors of its antidepressant benefit are lacking. While pre-treatment neurocognitive functioning has been shown to predict pharmacological antidepressant treatment outcome (e.g., Bruder et al. 2014), research on neurocognitive functioning as a predictor of CBT treatment outcome is less extensive. The current study examined the contribution of baseline neuropsychological functioning to the prediction of antidepressant outcome with CBT for Major Depressive Disorder (MDD). We hypothesized that depressed participants who were more neurocognitively intact would respond better to the structured approach of CBT.

Methods: 31 unmedicated MDD patients completed a comprehensive neuropsychological battery before initiation of 14 CBT sessions. A subgroup also completed a probabilistic reversal learning task, designed to assess mental flexibility. Depression severity was assessed with the Beck Depression Inventory (BDI). Remitters (>50% reduction in BDI; final BDI<10) were compared to non-remitters.

Results: Remitters performed generally worse across all items in the baseline neuropsychological battery considered simultaneously ($F[1,28]=6.82$, $p=0.01$). Univariate post-hoc testing showed a significant difference only on the Continuous Performance Test ($t[28]=-3.94$; $p<0.001$). The remitters completing a reversal learning task also performed more poorly, with a significant difference in errors during the probabilistic maintenance phase.

Conclusions: These results suggest that the structured approach of CBT may particularly benefit individuals with mild depression-related cognitive difficulties—especially sustained attention difficulties—during a depressive episode. Further research is needed to examine the potential contribution of these neurocognitive domains to the mechanisms of CBT efficacy, and the specificity of these prediction findings to CBT.

Supported By: This work was supported by the National Institute of Mental Health Clinical Investigator Award: K08 MH085061.

Keywords: Depression, Cognitive Behavioral Therapy, Remission, Neurocognitive Predictors, Attention

S158. Relationship Between Childhood Adversity and Impulsivity in Major Depression and Bipolar Types I and II

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Background: Impulsivity in mood disorders has been associated with increased risk for substance misuse and suicide. Childhood adversity is a common risk factor for impulsivity in mood disorders. To date, there is a paucity of data regarding the predictors of impulsivity, such as childhood adversity, among mood disorders. Aim: To examine the prevalence of impulsivity in patients with major depression (MDD), bipolar type I (BPI) or bipolar type II (BPII). To examine childhood adversity as a modifier of the association between impulsivity and mood disorder type.

Methods: 225 participants were recruited from the McGill University Health Center in Montreal, Quebec. Mood diagnoses were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Barrett's Impulsivity Scale (BIS) was used to assess impulsivity in the attentional, motor and non-planning domains. Childhood adversity was assessed using the Childhood Experiences of Care and Abuse Questionnaire (CECA-Q). ANOVA and Kruskal-Wallis tests and linear regression models were conducted.

Results: Impulsivity in the attentional ($p=0.017$) and non-planning ($p=0.051$) domains was greater in BPII than MDD and BPI. When childhood adversity is examined, maternal psychological abuse is associated with greater impulsivity in both attentional ($\beta=0.992$, $p=0.037$) and motor ($\beta=1.253$, $p=0.022$) domains, after controlling for mood disorders. For impulsivity in the non-planning domain, the association between mood disorder type was accounted for by (1) maternal psychological abuse ($\beta=0.681$, $p=0.031$) and (2) maternal physical abuse ($\beta=-0.768$, $p=0.026$).

Conclusions: Childhood adversity, especially maternal psychological abuse, accounts for the differences in mood disorders types and impulsivity.
Keywords: Bipolar Disorders, Impulsivity, Childhood Adversity

S159. Investigating the Clinical Predictors of Depression in Huntington's Disease

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Background: Huntington's disease (HD) is a fatal neurodegenerative disease. HD is characterized by motor dysfunction and behavioral abnormalities. Depression is of great relevance as it is considered a significant burden for both individuals with HD and their caregivers. Also, the presence of depression is a predictor of suicidality. Despite the high frequency of depression in HD, there is a lack of data to guide clinicians in its management. This study investigates clinical predictors of depression in HD patients.
Methods: This study included 2,303 subjects with manifest HD from the Enroll-HD Database (December, 2015). A binary logistic regression (backward stepwise approach) was performed to ascertain the effects of general clinical characteristics, medical history of substance use and psychiatric/behavioral problems, motor and functional capacity and cognitive performance on the likelihood that subjects with HD present depression or suicidal ideation.
Results: In the model ($\chi 2 = 270.648$, $p < 0.0001$), younger age at HD clinical diagnosis (OR=0.969, p=0.001), lower number of CAG repeats (OR=0.904, p=0.002), clinical history of irritability (OR=2.119, p<0.0001), violent/aggressive behavior (OR=1.492, p=0.040), apathy (OR=3.631, p<0.0001), psychosis (OR=3.658, p=0.001) and cognitive impairment (OR=1.409, p=0.024)], and female sex (OR=2.124, p<0.0001) remained as predictors on the likelihood of depression. Additional analyses revealed that depression was significantly associated with suicidal ideation (52.2% of subjects HD presenting history of depression had suicidal ideation, p<0.0001).
Conclusions: Depression is associated with a younger age at motor manifestations and a lower number of CAG repeats. Female sex, behavioral problems and poorer cognitive performance were also predictors for depression in HD.
Keywords: Depression, Huntington's Disease, Suicidality, Predictors

S160. Antidepressant Effects of Single and Repeated Ketamine Infusions in Treatment-Resistant Depression

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Background: Unmet needs for the treatment of depression include drugs with rapid therapeutic action and superior response and remission rates. Subanaesthetic doses of ketamine may meet both of these needs. The objectives of this study were to examine the antidepressant effects of single and repeated ketamine infusions and prolongation of antidepressant response.
Methods: Forty participants with treatment-resistant depression (TRD) completed a single-centre trial of ketamine. Participants first received a single ketamine infusion administered during a double-blind cross-over with midazolam (an active placebo). Following relapse of depressive symptoms, participants received 6 open-label ketamine infusions administered thrice-weekly over two weeks. Ketamine responders received 4 further open-label ketamine infusions administered once-weekly (maintenance phase). Depressive symptoms were evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR).
Results: Participants had a greater decrease in MADRS scores 24 hours after a single infusion of ketamine compared to midazolam ($p < .001$). At 24-hours post-infusion, 27% of participants met response criteria (50% decrease in MADRS scores). Repeated ketamine infusions had cumulative antidepressant effects with MADRS scores decreasing with each infusion ($p < .001$). The overall response rate following repeated infusions was 56%. Among responders, there was no further change in MADRS scores with weekly infusions ($p = .79$). QIDS-SR outcomes were equivalent.
Conclusions: A single ketamine infusion elicited rapid antidepressant effects. Repeated ketamine infusions have cumulative antidepressant effects. Antidepressant response was maintained with once-weekly maintenance infusions. Ketamine shows promise for improving response times and rates for individuals with TRD.
Supported By: Canadian Institutes of Health Research (CIHR)
Keywords: Ketamine, Major Depressive Disorder (MDD), Treatment-Resistant Depression, Antidepressant Response, Repeated Infusions

S161. Hydrogen Sulfide Improves the Depressive-Like Behavior of Rats by Increasing the Surface Expression of AMPArs

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Background: Hydrogen sulfide (H2S) has been recognized as the toxic gas with a characteristic smell of rotten eggs for centuries, which has been identified as an endogenous modulator of tissue function. A previous study preliminarily reported H2S might improve depressive-and anxious-like behaviors tested in non-stressed rats and mice. We asked whether H2S provided fast antidepressant effect on major depressive disorders and the underlying mechanisms.
Methods: To clarify the action and underlying mechanisms of H2S on the depression-like behavior, we observed the effect of intraperitoneal injection of H2S donor NaHS or inhaled H2S on the depression-like behavior in the chronic unpredictable mild stress (CUMS) model. The role of mTOR signaling pathway and

glutamate receptor in the antidepressant effect of H2S was evaluated.
Results: The decreased level of H2S was detected in the hippocampus of chronic unpredictable mild stress (CUMS)-treated rats. Acute administration of H2S either by H2S inhalation or by the donor NaHS produced a rapid antidepressant-like behavioral effect. Further investigation demonstrated that this effect of H2S was mediated by reversing the CUMS-induced decrease in dendritic spine density and required the activation of mTORC1 and neurotrophic TrkB receptors, proceeded to increase synaptic protein expression including PSD95, synaptophysin, and AMPA receptor GluR1/2 subunit.
Conclusions: Our results demonstrate that H2S activates mTORC1 signaling cascades, and thereby produces fast-onset antidepressant effect. The study provides a profound insight into H2S or its donors as potent preventive and therapeutic agents for intervention of depression.
Supported By: NSFC
Keywords: Hydrogen Sulfide, Depression, AMPA receptor

S162. Antidepressant and Pro-Cognitive Effects of a Novel Series of GABA-A Receptor Positive Allosteric Modulators With α5 Subunit Efficacy Properties

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Background: Altered signaling of GABA is frequently reported in multiple psychiatric disorders, and in normal and pathological ageing. Reduced function of GABA Dendritic Targeting Interneurons (DTI) contribute to cognitive and mood symptoms. α5-containing GABA-A receptor mediate the function of GABA-DTI, hence, we hypothesize that enhancing α5-containing GABAA receptor activity will alleviate mood and cognitive symptoms in neuropsychiatric diseases and aging.
Methods: Our group developed three new compounds targeting α5-containing GABA-A receptor. To validate high potentiation at these receptors, electrophysiology recordings were performed in HEK-293T cells. Pharmacokinetic and pharmacodynamic profiles were obtained in mice at different doses (1, 5 and 10mg/kg). Multiple preclinical behavioral assays were used to attest for anxiety-like phenotype (plus maze), behavioral despair (forced swim test), locomotor activity and working memory performance (spontaneous alternation).
Results: All three compounds showed potentiation at the α5, but also at the α1 subunit. They were stable in the plasma and in the brain. At the behavioral levels, all three compounds exhibited increased time in the open arms of the plus maze, decreased immobility in the forced test and did not have an effect on locomotor activity. Notably, 2 of the 3 compounds restored stress-induced or age-related cognitive deficits.
Conclusions: We demonstrated that our new compounds were stable in mice, potentiate the α5 and α1-containing GABAA receptors. Our lead compound shows robust therapeutic effects (pro-cognitive efficacy, antidepressant and anxiolytic properties without sedation) and desirable pharmacokinetic and toxicological profiles in rodents, making it a good candidate for drug development.
Keywords: GABA-A, PAM, Cognition, Depression, Mouse Model

S163. Rapastinel, a Rapid-Acting Antidepressant, Does Not Adversely Affect Cortical Network Oscillations: A Quantitative Electroencephalography Study in Rats

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Background: Rapastinel (GLYX-13, AGN-241659) is a rapidly acting N-methyl-D-aspartate receptor (NMDAR) modulator with partial agonist properties in development for major depressive disorder. In rodents, NMDAR antagonists, such as ketamine, increase high-frequency gamma oscillations, an electrophysiological effect correlated with acute psychosis. Here, the effects of rapastinel and ketamine on cortical network oscillations were evaluated in rats using quantitative electroencephalography (EEG).
Methods: Rats (n=14) were surgically implanted with cortical electrodes for EEG. Using a cross-over treatment design, rats were injected with antidepressant doses of rapastinel (3, 10, or 30 mg/kg, IV) or ketamine (30 mg/kg, IP) and telemetric outputs of a 60 min test were quantitatively analyzed under vigilance-controlled and uncontrolled conditions. Mean percent change in absolute cortical spectral power versus control was calculated in 5 sub-frequency bands (delta: 1-4; theta: 4-8; alpha: 8-13; beta: 13-36; gamma: 36-64 Hz) and analyzed using the Wilcoxon signed-rank test (two-tailed).
Results: Under vigilance-controlled conditions, rapastinel 30 mg/kg slightly but significantly decreased mean cortical spectral power in the alpha band (91.8% of control; $P<.05$); under vigilance-uncontrolled conditions, rapastinel 10 mg/kg weakly but significantly increased power in the beta band (104.4% of control; $P<.05$). Ketamine increased power in the gamma band under vigilance-controlled (148.4% of control; $P<.05$) and uncontrolled (147.1% of control; $P<.05$) conditions and at all time points ($P<.05$). No mean effects of rapastinel or ketamine were observed at other frequency ranges.
Conclusions: Unlike ketamine, there was no consistent effect of rapastinel on network oscillations at any frequency range, suggesting that rapastinel may lack hallucinogenic/psychotomimetic potential.
Supported By: Allergan
Keywords: Major Depressive Disorder (MDD), Rapastinel, Electroencephalography (EEG)

S164. GABAergic Dysfunction in the Chronic Mild Stress Model: Modulation by Lurasidone Treatment

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Background: Exposure of rats to chronic stress is able to produce functional alterations that are associated with different psychiatric disorders, which may be target of pharmacological intervention. The aim of the present study was to investigate the ability of a chronic treatment with lurasidone in normalizing the behavioral and molecular changes produced by chronic mild stress (CMS) in rats.
Methods: Adult male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to identify rats that were susceptible to the manipulation. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure (n=10/experimental group). Animals were tested for anhedonia and for cognitive impairment before being sacrificed for the dissection of brain regions to be used for the molecular analyses.
Results: CMS produced a significant reduction of sucrose intake (-49%, $p<0.001$) as well as cognitive impairment, which were normalized by chronic lurasidone treatment. Rats exposed to CMS also display a significant reduction of parvalbumin expression in dorsal hippocampus (-58%, $p<0.001$), an effect that was associated with a dysregulation of redox mechanisms. Interestingly these abnormalities were counteracted by chronic lurasidone administration
Conclusions: Our results demonstrate that exposure to CMS produces functional and molecular alterations, which are relevant for different 'domains' of psychiatric disorders. We show that lurasidone treatment is capable of normalizing such changes and may therefore promote resilience toward adverse environmental conditions, such as stress, which represents a major vulnerability element in the etiology of mental illness.
Supported By: Project funded by Sumitomo Dainippon Pharma
Keywords: Chronic Stress, Parvalbumin Interneurons, Oxidative Stress, Dorsal Hippocampus, Cognitive Impairment

S165. ALKS 5461: Affinity, Potency, and Functional Activity of Buprenorphine and Samidorphan Alone and in Combination

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Background: ALKS 5461, a combination of buprenorphine and samidorphan, is being evaluated as an adjunctive treatment for major depressive disorder. However, the receptor binding properties and the in vitro activity of these two compounds alone and in combination have not been characterized previously.
Methods: [3H]Buprenorphine and [3H]samidorphan binding to membranes from CHO cells stably expressing the human mu(MOR), kappa(KOR) and delta(DOR) opioid receptors was performed. The [35S]GTPgammaS binding assay was used to show the in vitro activity of buprenorphine and samidorphan alone and in combination. Bioluminescent resonance energy transfer (BRET) assay with luciferase and green fluorescent protein-fused donor/acceptor pairs was used to study buprenorphine and samidorphan, alone and in combination, activating opioid receptors to interact with specific G proteins and to recruit beta-arrestin.
Results: [3H]Buprenorphine and [3H]samidorphan bound to all three opioid receptors with high affinity (Kd values of 3 nM or less). [3H]Buprenorphine had a very slow dissociation from the MOR. Both the [35S]GTPgammaS binding and BRET assays showed that buprenorphine was a partial agonist at all three opioid receptors. Samidorphan was an antagonist at the MOR and a partial agonist at the KOR and DOR, coupled to the Gi protein. The combination of buprenorphine and samidorphan at a fixed ratio, corresponding to plasma levels of the two compounds in ALKS 5461-treated subjects, showed that samidorphan decreased buprenorphine's activity and ability to recruit β-arrestin to the MOR.
Conclusions: ALKS 5461 may produce its physiological effects by attenuating the functional activity of buprenorphine and its ability to recruit β-arrestin to the MOR.
Supported By: Alkermes, Inc.
Keywords: Opioid Receptor, Receptor Binding, G Proteins, BRET, GTPgammaS

S166. Intravenous Infusion of Xenon-Containing Echogenic Liposomes Generates Rapid Antidepressant-Like Effects

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Background: Similar to ketamine, xenon gas acts as a glutamatergic N-methyl-D-aspartate receptor antagonist, and produces promising anesthetic and neuroprotective effects. Herein, we formulated xenon gas into a liposomal carrier (15 μl/mg) called xenon-containing echogenic liposomes (Xe-liposome) for systemic delivery, and investigated its effect as an antidepressant studying synaptic biomarkers including brain-derived neurotrophic factor (BDNF), protein kinase B (AKT), mammalian target of rapamycin (mTOR), protein kinase C (PKC) and extracellular signal-regulated kinase-1/2 (ERK1/2) in blood and brain.
Methods: One-hour after Xe-liposome infusion, animals were assessed for depression-like behaviors using a forced swimming test (FST), and spontaneous locomotor activity. Blood was obtained, as well as frontal cortex and hippocampal sample for immunoblotting and/or enzyme-linked immune sorbent assays.

Results: Acute intravenous infusion of Xe-liposome, at 6 mg/kg, showed an increase in swimming time in the FST ($p<0.006$), indicating antidepressant-like phenotypes. Higher doses of Xe-liposomes (9 mg/kg) failed to improve swimming duration. Gross locomotor locomotion remained similar for both the doses. The inverted U-shaped dose-response pattern was also reflected in the biochemical results. In frontal cortex tissue analyses, increased protein levels of BDNF (64%), and enhanced phosphorylation of AKT (43%) and mTOR (93%) was observed at the 6 mg/kg dose level of Xe-liposomes, while these biomarkers and phosphorylated PKC and ERK1/2 levels remained unchanged at the higher dose. Moreover, Xe-liposomal treatment did not change the plasma and protein levels of BDNF, and phosphorylated AKT, mTOR, PKC and ERK1/2 hippocampal expressions.
Conclusions: Xe-liposomes mediate a rapid antidepressant-like effect through activation of AKT/mTOR/ BDNF signaling pathway.
Keywords: Xenon, Depression, Forced Swimming Test, BDNF, mTOR

S167. Chronic Stress-Induced Depression Impairs Contractile Activity of Rat vas Deferens: Effect of Infliximab Treatment

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Background: In animals, unpredictable stressors have been shown to induce depressive-like behavior and changes in sexual behavior. Inflammation has been reported as an imperative phenomenon in neuropsychiatric disorders, including depressive behavior. The aim of this study was to investigate the effects of infliximab (a TNF-alpha inhibitor) on contractile activity of vas deferens in unpredictable chronic mild stress (UCMS)-exposed depressive rats.
Methods: Male Wistar rats were divided into control, UCMS-exposed and infliximab-treated UCMS-exposed groups. Different stressors were applied to UCMS-exposed rats in an unpredictable way during 5 weeks and infliximab was applied (5 mg/kg/week; i.p.) at the same period. Forced swimming test (FST) was used to evaluate the depressive-like behavior of animals. After 5 weeks, vas deferens tissues were surgically removed and, noradrenaline- (10-8-10-4 M), and ATP- (10-8-10-4 M) induced contractile responses were evaluated in isolated organ baths. Significant differences were determined using one-way ANOVA followed by Tukey post hoc tests. $p<0.05$ was considered significant.
Results: In the FST, UCMS-exposed rats displayed more immobility than control rats ($p<0.05$), while there was no difference between infliximab-treated rats and control rats in terms of immobility time ($p>0.05$). Noradrenaline- and ATP-induced contractile responses were significantly inhibited in the vas deferens obtained from the UCMS-exposed group ($p<0.05$) and infliximab treatment significantly improved the contractile responses in UCMS-exposed rats ($p<0.05$).
Conclusions: Our results demonstrated that impaired contractile responses of vas deferens in UCMS-exposed rats were improved by infliximab treatment, suggesting that targeting TNF-α may be an effective strategy in preventing male reproductive system disabilities in chronic stress-induced depression.
Supported By: This research was supported by a grant from Kocaeli University, Scientific Research Project-BAP 2017/074.
Keywords: Unpredictable Chronic Mild Stress, Depression, Male Reproductive System, Vas Deferens, Inflammation

S168. Beneficial Effects of Etanercept on Depressive-Like Behaviors in Streptozotocin-Induced Diabetic Rats

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Background: A number of pathophysiological mechanisms have been reported to link diabetes and depression. Recently, inflammation-related process has been implicated in the development of both diabetes and depression. Therefore, the aim of the current study was to analyze the effects of etanercept on depressive−like behaviors in streptozotocin-induced diabetic rats.
Methods: Male Wistar rats were divided into three groups ($n=7$ in each group): Control, diabetic (50 mg/kg/i.p. streptozotocin) and etanercept-treated diabetic group. Rats from etanercept-treated diabetic group received 0.8 mg/kg/week of etanercept subcutaneously after induction of diabetes for 4 weeks. After 4 weeks, locomotor activity test was used to evaluate the locomotion of rats. Also, forced swimming test (FST) was used to evaluate the depressive-like behavior of animals. Significant differences were determined using one-way ANOVA followed by Tukey post hoc tests. $p<0.05$ was considered significant.
Results: Four weeks after streptozotocin injection, diabetic and etanercept-treated diabetic rats exhibit significantly increased blood glucose levels as compared to the control rats ($p<0.05$). In the locomotor activity test, no significant differences were observed between the groups ($p>0.05$). In the FST, there were differences between groups in terms of immobility time during second day of testing. Diabetic rats exhibited more immobility than nondiabetic rats ($p<0.05$). There was no difference between etanercept-treated diabetic rats and nondiabetic rats.
Conclusions: Our results showed that etanercept exhibited antidepressant-like effect in diabetic rats, indicating that inflammation process has an important role on depressive like behavior in diabetes. Furthermore, the antidepressant effects of etanercept were independent of hyperglycemia.
Keywords: Diabetes, Inflammation, Depression, Neuroinflammation, Behavior

S169. SAGE-516 Ameliorates Depression-Like Behaviors and Improves Maternal Care in Preclinical Models of Postpartum Depression

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Background: Investigation into the pathological mechanisms underlying postpartum depression (PPD) and preclinical testing of potential treatments for PPD has been hindered by the lack of animal models of such a complex disorder. Our laboratory has characterized two preclinical mouse models of PPD, mice lacking δ subunit-containing GABAA receptors (GABAARs) (Gabrd-/- mice), and mice lacking the K+/Cl- co-transporter, KCC2, specifically in corticotropin-releasing hormone (CRH) neurons (KCC2/Crh mice). These studies established two unique mouse models which serve as useful tools for testing novel therapeutic compounds.
Methods: Gabrd-/- mice, KCC2/Crh mice and wild type littermate controls were provided with either standard, SAGE-516 (450mg/kg), or clobazam (250mg/kg) chow from day 14-21 of pregnancy and depression-like behaviors and maternal care was assessed using the forced swim test and maternal approach test, respectively, at 48 hours postpartum.
Results: Here we demonstrate that SGE-516 treatment decreases depression-like behaviors in Gabrd-/- and KCC2/Crh mice, evident from the increased latency to immobility and decreased total time immobile in the forced swim test. SGE-516 also improves maternal care in the maternal approach test, decreasing the latency to approach and increasing the total interaction time with their pups. In contrast, treatment with the benzodiazepine, clobazam, was ineffective at decreasing postpartum depression-like behaviors or improving maternal care.
Conclusions: These findings demonstrate that SGE-516 is effective at ameliorating postpartum depression-like behaviors and improving maternal care in two independent preclinical models of PPD. Further, these studies validate the use of these preclinical models in testing the therapeutic potential of novel treatments for PPD.
Supported By: SAGE Therapeutics; NINDS RO1 NS073574 (J.M.) and NS102937 (J.M.); NIH-NIGMS K12GM074869.
Keywords: Postpartum Depression, Allopregnanolone, GABAergic Neurosteroid, GABA-A, KCC2

S170. In Vivo Characterization of an Orally Available, Brain Penetrant Small Molecule GPR139 Agonist

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Background: Recently, our group along with another deorphanized GPR139 as having the endogenous ligands L-Phenylalanine and L-Tryptophan. GPR139 is discretely expressed in brain, with highest expression in medial habenula. Not only are the endogenous ligands catecholamine/serotonin precursors, but GPR139 expressing areas can directly/indirectly regulate the activity of catecholamine/serotonin neurons. Thus, GPR139 appears expressed in an interconnected circuit involved in mood, motivation, and anxiety. The aim of this study was to characterize a selective and brain penetrant GPR139 agonist (JNJ-63533054) in relevant models.
Methods: JNJ-63533054 was tested for its effect on c-fos and on basal levels of serotonin, norepinephrine, or dopamine in rat brain, and in behavioral models of mood and anxiety.
Results: The agonist did not alter c-fos expression in medial habenula nor neurotransmitter levels in prefrontal cortex or nucleus accumbens. The agonist produced an anhedonic-like effect on urine sniffing, but had no significant effect in tail suspension, with no interaction with imipramine, no effect on naloxone place aversion, and no effect on learned helplessness. In the marble burying test, the agonist produced a small anxiolytic-like effect, with no interaction with fluoxetine, and no effect in plus maze.
Conclusions: GPR139 has high expression in medial habenula, an area with connections to limbic and catecholaminergic/serotoninergic areas. However, a GPR139 agonist had no effect on c-fos in medial habenula, did not alter catecholamine/serotonin levels, had no behavioral interaction with catecholamine/serotonin uptake blockers in the models tested, and had negligible effects on behaviors commonly associated with these pathways.
Keywords: Novel Drug Targets, Animal Behavior, Phenylalanine, Tryptophan

S171. Samidorphan in Combination With Buprenorphine Improves Behavioral Deficits in Non-Clinical Tests of Depression and Anxiety Using SSRI Insensitive Rats

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Background: ALKS 5461, a combination of buprenorphine (BUP) and samidorphan (SAM), is an opioid system modulator under development as an adjunct treatment for MDD patients with inadequate response to conventional antidepressants. Here, we study the behavioral effects of the combination of BUP and SAM, alone and together, with a selective serotonin reuptake inhibitor (SSRI) in the Wistar Kyoto (WKY) rat strain, a model that mimics some aspects of depression and anxiety and is reportedly insensitive to SSRI treatment.
Methods: To assess SSRI insensitivity, WKY rats (n=8/group) received acute or repeated fluoxetine or escitalopram (ESC) treatment before exposure to the forced swim test (FST). Both treatment-naïve and ESC-treated rats received a single subcutaneous injection of BUP:SAM before the FST. Separate cohorts of rats (n=8/group) were dosed acutely with diazepam (DZ), ESC or BUP:SAM 24h and were tested in the marble burying task to assess anxiolytic-like activity. Statistics: t-test, one-way or repeated measures ANOVA, followed by post hoc analysis where appropriate.
Results: In the FST, neither acute nor chronic SSRI treatment altered immobility compared to vehicle controls. Acute BUP:SAM significantly reduced immobility in both naive ($p<0.05$) and ESC-treated rats ($p<0.01$). BUP:SAM significantly reduced marble burying behavior 24h post injection ($p<0.01$), whereas DZ and ESC were inactive under these treatment conditions.
Conclusions: Our data indicate that WKY rats are SSRI-insensitive when tested in the FST, and therefore may be a useful model for investigating novel antidepressants. Our data also show that BUP:SAM-mediated opioid system modulation

improves behavioral deficits in non-clinical tests of depression and anxiety.
Supported By: These studies were funded by Alkermes, Inc.
Keywords: ALKS 5461, Buprenorphine, Depression, Escitalopram, Anxiety

S172. Characterizing Individual Variation in Multi-Modal Thalamic Connectivity and Behavior

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Background: Abnormalities in both structural and functional connections between distinct brain regions have been identified in multiple neuropsychiatric disorders and are thought to play an important role in the pathophysiology of psychosis. In particular, disruptions in the connectivity of associative thalamic circuits have been robustly demonstrated in psychosis spectrum disorders, suggesting that such disruptions may underlie behavioral traits in individuals. However, it remains unknown whether individual variation in both structural and functional thalamic connectivity map to specific behavioral traits.
Methods: We examined the relationship between measures of cognition and behavior and combined multi-modal thalamic dysconnectivity in a sample of 334 healthy young adults, using multivariate statistics. Multi-modal connectivity was characterized using functional connectivity of resting-state fMRI and probabilistic diffusion weighted imaging (DWI)-derived tractography of functional thalamic nuclei. Neuroimaging and behavioral data were acquired and processed by the Human Connectome Project.
Results: Results reveal distinct maps of association between cognitive performance and functional and structural connectivity with associative versus sensory-motor thalamus. Additionally, these results indicate that a multivariate analysis of multi-modal imaging data can be used to concurrently map structural and functional connectivity in relation to subject-specific cognitive performance.
Conclusions: This study is one of the first to examine individual variation in thalamic connectivity and cognition using concurrent multi-modal approaches. These results suggest that combining information from multiple complementary brain imaging modalities can provide additional insight into the association between neural connectivity and behavior, with implications for identifying neural substrates for trait-like markers of psychiatric disease.
Supported By: National Institutes of Health
Keywords: Multimodal Imaging, Cognition, Thalamus

S173. Evaluation of a Potent and Selective PET Radioligand to Image COX-1 in Human and Nonhuman Primates

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Background: Cyclooxygenase (COX)-1 is generally considered a constitutive enzyme that serves a role in normal function, but studies have demonstrated that it also contributes to proinflammatory responses, particularly in brain. Developing in vivo COX-1 activity measurements would permit definitive studies in healthy and inflammatory conditions. Towards this end, our laboratory recently developed 11C-PS13, a potent and selective PET radioligand for COX-1. This study sought to determine whether 11C-PS13 can selectively image constitutive levels of COX-1 in human and nonhuman primates.
Methods: Dynamic whole-body PET data were obtained using 11C-PS13 in 16 scans with rhesus monkeys and three scans with humans. To confirm that uptake was specifically associated with COX-1, pharmacological blockade studies were also performed with non-radioactive drugs preferential for COX-1 or COX-2 in seven scans with rhesus monkeys and six scans with humans. Venous blood samples were collected at four time points during the scan to measure the concentrations of parent radioligand and radiometabolites.
Results: In rhesus monkeys, 11C-PS13 showed specific uptake in several organs, including spleen, gastrointestinal tract, kidneys, and brain. 11C-PS13 uptake in these organs was blocked by COX-1 preferential inhibitors (PS13, aspirin, and ketoprofen), but not by COX-2 preferential inhibitors (MC1 and celecoxib). In healthy human subjects, organ uptake paralleled that in monkeys and was similarly displaced in preferential fashion by aspirin over celecoxib.
Conclusions: 11C-PS13 can be used as a quantitative in vivo measure of COX-1 in human and nonhuman primates. 11C-PS13 may also help elucidate the role of COX-1 in neuroinflammatory disorders.
Supported By: This study was funded by the Intramural Research Program of the National Institute Mental Health, NIH: project ZIAMH002852.
Keywords: PET Imaging, Inflammatory Markers, Cyclooxygenase, Neuroinflammation, Biomarkers

S174. Remotely Programmed Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Intractable Obsessive Compulsive Disorder

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Background: Treatment refractory obsessive-compulsive disorder (OCD) is a disabling condition. Deep brain stimulation (DBS) of the ventral capsule/ventral striatum(VC/VS) has demonstrated safety and effectiveness for severe, chronic, treatment-resistant OCD. However, programming is a crucial

aspect of DBS that requires laborious titration to set optimal parameters.
Methods: We use a novel DBS system capable of remote and wireless programming via the internet for two OCD patients. Two weeks after ventral capsule/ventral striatum DBS implantation, initial programming followed by biweekly programming was conducted via the internet. Yale-Brown Obsessive Compulsive Scale (YBOCS) score was the main outcome measure.
Results: The study included two patients treated for approximately three months at this time. So far, the YBOCS scores (40 in total) of the two patients have decreased, from 31 to 18 (4.5v, 90us, 130Hz, Case+1-3-, Case+5-7-) for one patient, and from 40 to 35 (5v, 90us, 130Hz, Case+1-2-, Case+5-6-) for the other. There have been no specific adverse events with remote programming as yet.
Conclusions: Remote programming of DBS can markedly improve patient convenience and minimize total treatment time, while enabling optimal parameter adjustment as effectively as conventional DBS in OCD without introducing additional side effects. However, the optimal programming parameters for each patient have not been found due to limited time.
Supported By: National Natural Science Foundation of China Grant (81771482), Shanghai Jiao Tong University School of Medicine-Institution of Neuroscience (SHSMU-ION) Research Center for Brain Disorders (to B.M.S.)
Keywords: Neuromodulation, Deep Brain Stimulation, Obsessive Compulsive Disorder (OCD), Yale-Brown Obsessive Compulsive Scale

S175. Open Board

S176. Open Board

S177. Lower Trust Scores of Ambiguous Facial Expressions Associated With Increased Electrocortical Activity

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Background: Negativity bias is the tendency to interpret neutral or ambiguous events and stimuli (e.g., neutral facial expressions) as negatively. Individual differences in negativity bias, as well as higher negativity bias, has been observed in patients with depression and anxiety. The current study aims to test whether a negativity bias is present while individuals judge the trustworthiness of neutral faces, as well as in brain responses to these facial expressions.
Methods: Participants completed an emotional faces appraisal task which involved viewing and subsequently rating the trustworthiness (0-100 scale: 0 = not trustworthy, 100 = trustworthy) of three types of emotional facial expressions: fear, happy, neutral. Simultaneous electroencephalography (EEG) was collected with a focus on the late positive potential (LPP), an event-related potential (ERP) associated with the magnitude of emotional salience.
Results: Results showed that neutral faces were rated as less trustworthy (43.31±14.68) compared to both fearful (47.94±14.37) and happy faces (61.81±12.40), p's < 0.05. Further, LPP mean activity did not significantly differ between neutral and fearful or happy faces; however, individuals with lower trustworthiness ratings for neutral faces showed larger LPP mean activity in frontal (1.88 μV±3.46), central (3.61 μV±3.14), and parietal brain regions (4.91 μV±3.38).
Conclusions: Together, these results suggest that neutral faces may not be interpreted as 'neutral', and that trustworthiness of neutral expressions is related to the amount of emotion-related neural processing. These results have further implications for both trust and interpersonal relationships.
Supported By: NIH Award Numbers GM118981, GM118982, GM118983
Keywords: Emotional Facial Expressions, Electroencephalography (EEG), LPP, Emotion Perception

S178. Blue Light Therapy Improves Executive Function Following Mild Traumatic Brain Injury

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Background: Sleep problems and circadian disruption are common following mild traumatic brain injury (mTBI) and may affect recovery from the injury. Because the circadian regulation of sleep is strongly regulated by exposure to light, we hypothesized that daily morning treatment with blue-wavelength light would improve circadian entrainment, sleep, and executive functioning in patients recovering from mTBI.
Methods: Patients with a recent mTBI (16 female; Age=23.3, SD=7.2) underwent blue (469 nm; n=16) or amber (478 nm; n=15) morning light therapy for 30-minutes daily for 6-weeks. At baseline and post-treatment, participants completed a 10-trial version of the Tower of London (TOL), an executive function task requiring planning and sequencing. The number of moves made to complete the puzzles and the time per move were recorded by computer.
Results: A throughput metric was calculated that accounts for time and accuracy (i.e., the number of correct bead placements per minute). There was a significant light condition x session interaction (p=.016). Specifically, BLT was associated with a significant pre-to post-treatment increase in TOL throughput (p<.0001), whereas ALT showed no significant improvement (p=.094).
Conclusions: Six weeks of daily morning exposure to blue-wavelength light led to improved planning and sequencing ability on the TOL. These findings are consistent with recent evidence suggesting that BLT can reduce fatigue, improve sleep timing, and facilitate brain repair processes among patients recovering from concussion. Additional research is needed to determine whether these findings are caused by changes in sleep or other factors.
Supported By: USAMRMC (W81XWH-11-1-0056)
Keywords: mTBI, Blue Light, Executive Functioning, Sleep, Circadian Rhythms

S179. Prevalence of NMS-Like Features in Anti-NMDA Receptor Encephalitis

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Background: Anti-NMDA receptor encephalitis (anti-NMDArE) demonstrates a strong predilection for women, and most afflicted individuals are first treated by a psychiatrist because they appear to have primary psychiatric disorders for which antipsychotic medications are likely to be prescribed. However, anti-NMDArE often manifests clinical signs that can be mistaken for neuroleptic malignant syndrome (NMS), further confounding diagnosis and delaying the treatment that is needed to avoid serious disability. The purpose of this study was to estimate the prevalence of NMS-like clinical features in anti-NMDArE.
Methods: Systematic searches of PubMed and EMBASE databases were executed to find all published reports of anti-NMDArE with behavioral or psychiatric symptoms.
Results: The searches identified 185 women with mean(S.D.) age 29.4(10.3) years. Fifty-four (29.2%) patients had fever, 91 (49.2%) had one or more signs of dysautonomia, 133 (71.9%) had evidence of altered mental status, and 93 (50.3%) had signs of increased muscle tone or rigidity, or catatonic symptoms. One hundred sixty-four patients (88.6%) had at least one NMS-like feature: 46 (24.9%) patients had only one, 52 (28.1%) patients had two, 43 (23.2%) patients had three, and 23 patients (12.4%) had all four NMS-like features.
Conclusions: NMS-like clinical features are very likely to be observed in the course of anti-NMDArE. Fever and dysautonomia are much less frequent than is altered mental status, and this profile may assist in the differential diagnosis of anti-NMDArE and NMS.
Keywords: NMDA Receptor, Autoimmune Disorder, Neuroleptic Malignant Syndrome, Diagnosis

S180. High Parenteral Dosage of Thiamine Recommended for Management of Wernicke's Encephalopathy

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Background: Wernicke's encephalopathy (WE) is a medical emergency. The objective of this study is to systematically review the literature published within the past fifteen years pertaining to prophylactic and curative treatment of WE with thiamine.
Methods: A systematic literature search was performed using Medline to include all studies published between January 1st of 2000 and November 30th of 2017 (PRISMA criteria).
Results: Of the 316 abstracts identified, 20 were retained. The evidence on the use of prophylactic thiamine was quite heterogeneous. The use of thiamine in this context largely depended on the evaluation of an individual's risk of developing WE. Use of prophylactic thiamine in low-risk patients is not universally indicated. High-risk patients merit parenteral treatment with a recommended posology of 250 mg daily for 3 to 5 days. Intramuscular route is preferred in outpatient settings, whereas intravenous route is suggested for inpatients. In cases where diagnosis of WE is suspected or confirmed, a curative treatment with high-dose IV thiamine is warranted. The evidence is much clearer in this setting, with treatment regimens consisting of 500 mg IV 3 times daily for 3 to 5 days, followed by 250 mg IV daily for a minimum of 3 to 5 additional days, which is widely accepted in the literature.
Conclusions: The literature does indicate that thiamine should be prescribed at high dosages, with the parenteral routes indicated in hospital settings and in high-risk patients. Based on the current literature review, we suggest treatment algorithms guiding thiamine prescription for WE.
Keywords: Wernicke's Encephalopathy, Vitamin B1, Prophylaxis, Treatment

S181. Power Spectra Characteristics in Antisocial Individuals During Rest: A Network Analysis

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Background: Resting-state networks (RSNs) dynamics in antisocial individuals are characterized by functional abnormalities in the DMN that are directly related to the severity of psychopathic traits. However, the extended scope of disruptions in RSNs beyond the DMN in antisocial individuals and its relationship to psychopathic severity still remains to be investigated. To this aim, this study investigated differences in spectral power during rest between offenders with psychopathic traits (OPT) and healthy individuals (HI), as well as the contribution of psychopathic severity to RSN functioning.
Methods: RSNs were identified through Independent Component Analysis (ICA) analysis on fMRI data. Power spectra activity in each identified network was compared between OPT (N=122) and HI (N=29) with a series of ANOVAs. Psychopathic severity was measured using PCL-R scores and years of drug use and its contribution to activity amplitude in the RSNs was measured using hierarchical regressions.
Results: ICA analysis yielded 8 RSNs: DMN, ECN, salience, visual, basal ganglia, sensorimotor, language and auditory networks. Offenders presented lower power spectra in comparison to HI during low-frequency activity (0-0.1 Hz), as well as higher power spectra during high-frequency activity (0.1-0.25 Hz) in the DMN and ECN. Moreover, offenders presented consistently higher power spectra during high-frequency activity in all RSNs. Psychopathy severity and years of drug use were significantly related to signal amplitude in the ventral DMN.
Conclusions: These results suggest that OPT present functioning disturbances in all RSNs, the DMN and ECN being most dysfunctional. Moreover, our results suggest an interaction between deficits in self-oriented processes and psychopathy severity.
Supported By: RO1DA026932

Keywords: Psychopathy, Antisocial Behavior, Resting State Networks, fMRI Resting State, Independent Component Analysis

S182. Evidence That the Polygenic Risk Score for Neuroticism Does Not Moderate the Impact of Childhood Trauma on Neuroticism: A GxE Model

Boris Klingenberg[1], Sinan Guloksuz[2], Claudia Menne-Lothmann[1], Jeroen Decoster[3], Ruud van Winkel[3], Dina Collip[1], Philippe Delespaul[1], Marc De Hert[4], Catherine Derom[5], Evert Thiery[6], Nele Jacobs[7], Marieke Wichers[8], Lotta-Katrin Pries[1], Ozan Cinar[1], Lin Bochao[9], Jurjen Luykx[9], Jim van Os[10], and Bart Rutten[1]

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Background: Neuroticism is thought to result from both environmental factors, such as childhood adversities, and individual genetic architecture which consists of many genetic variants of small effect (single nucleotide polymorphisms [SNPs]). We, therefore, aimed to investigate—for the first time—whether the genetic vulnerability (polygenic risk score [PRS] for neuroticism) moderates the impact of childhood adversities (CA) on neuroticism.
Methods: Data were derived from a general population adolescent and young adult twin sample. The total sample included 617 (Monozygotic=190, Dizygotic=427). The Short Eysenck Personality questionnaire (EPQ: 12 items), was used to measure neuroticism. PRS were trained on the results from the Genetics of Personality Consortium. Multilevel regression analyses, taking into account observations nested within twin pairs, were used to analyze the moderating effect of PRS (p-value$<$0.05) on the association between CA (Childhood Trauma Questionnaire sum-score) and neuroticism (EPQ sum-score). All analyses were adjusted for age, gender and 2 principle components (covariate, covariate X environment and covariate X PRS).
Results: There was no G-E correlation. Both PRS (b=5976.81, p= 0.025, 95% CI=735.77-11217.85) and CA (b=0.08, p$<$0.001, 95% CI=0.051-0.11) predicted neuroticism in separate models. However, in the interaction model, neither the main effect of PRS on neuroticism nor the multiplicative interaction between PRS and CA was significant; while CA remained associated with neuroticism (b=0.07, p=0.005, 95% CI=0.02-0.12).
Conclusions: These results suggest that in the presence of childhood adversity the current cumulative genetic risk score for neuroticism has a negligible impact on the explained variance of the phenotypical expression of neuroticism.
Supported By: The authors would like to acknowledge that the East Flanders Prospective Twin Survey (EFPTS) is partly supported by the Association for Scientific Research in Multiple Births and that the TwinssCan project is part of the European Community's Seventh Framework Program under grant agreement No. HEALTH-F2-2009-241909 (Project EU-GEI).
Keywords: Gene x Environment, Neuroticism, Polygenic Risk Score, Childhood Adversity, Twins

S183. Cardiac Afferent Signals Augment Fear in Anxiety Inhibit Fear in Schizophrenia

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Background: Heart and brain are dynamically coupled, particularly in the context of emotional arousal. Arterial baroreceptor afferents signal physiological arousal from the strength and timing of heartbeats. We tested for aberrant coupling of emotions to afferent cardiac signals in specific clinical psychiatric disorders characterised by affective disturbance.
Methods: We tested 296 patients with diagnoses encompassing Anxiety (N=28), Depression (N=58), Depression and Anxiety (N=42), Borderline Personality Disorder (N=22), Bipolar Disorder (N=50), Schizophrenia (N=18), Affective Psychosis (N=23, matching the Schizophrenia group for medication), and N=55 Healthy Control Participants. Individual participants were randomly presented emotional and neutral faces (100ms), either at cardiac systole, during arterial baroreceptors firing to brain, or at diastole, between heartbeats when baroreceptors are quiescent. Participants rated the emotional intensity of the faces.
Results: There was a significant differentiating effect of cardiac cycle on fear processing as a function of diagnosis [F(7, 287)=2.47, p=0.018]. As previously noted, sensitivity to fear expressions was greater at cardiac systole (relative to diastole) in control participants [t(54)=-2.28, p=0.027]. Importantly, this cardiac facilitation of fear was amplified in Anxiety patients [t(26)=-3.51, p=0.002] and, strikingly, the reverse effect was observed in patients with Schizophrenia, where cardiac afferent signals reduced fear intensity relative to faces processed at diastole [t(17)=3.81, p=0.001].
Conclusions: Our findings show that cardiac afferent signals can shape emotion processing, with differentiating impact in Anxiety and Schizophrenia. These embodied mechanisms will inform novel treatment targets for major psychiatric disorders.
Supported By: This work was conducted with support from the European Research Council (Advanced Grant Adg 324150 CCFIB to HDC) and by a philanthropic donation form the Dr. Mortimer and Theresa Sackler Foundation
Keywords: Schizophrenia, Anxiety, Interoception, Baroreceptor

S184. Oxytocin Increases Gaze to the Eyes in Schizophrenia

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Background: Lack of eye contact in schizophrenia impedes social interaction and contributes to impaired social functioning. Intranasal oxytocin increases gaze to the eye region of faces in healthy and autistic individuals, but oxytocin's effects on eye gaze in schizophrenia are unknown. We examined the effect of oxytocin on gaze to eyes in people with and without schizophrenia.
Methods: 32 men with schizophrenia (SZ) and 37 matched healthy controls (HC) completed an eye-gaze task after receiving 40 IU oxytocin or placebo in a double-blind, placebo-controlled, cross-over study. Participants passively viewed 20 color photographs of emotional faces and eye gaze patterns were tracked. We assessed attachment anxiety and SZ symptom severity as purported moderators using linear mixed-effects models.
Results: In the placebo condition, SZ gazed to eyes less than HC ($p = .047$). Oxytocin significantly increased gaze to eyes in SZ but significantly decreased gaze to eyes in HC ($p = .002$). Attachment anxiety interacted with drug condition such that attachment anxiety was more strongly positively associated with gaze to eyes in oxytocin versus placebo regardless of group ($p = .011$). In SZ, symptom severity interacted with drug condition such that greater symptom severity was more strongly positively associated with gaze to eyes in oxytocin versus placebo ($p = .003$).
Conclusions: Oxytocin might improve eye contact in SZ, potentially treating an underlying cause of social deficits. Higher attachment anxiety and greater symptom severity predicted oxytocin response, indicating that individual differences moderate oxytocin effects and must be considered in future work.
Supported By: Career Development Award (CDA) 1IK2CX000758-01A1
Keywords: Schizophrenia, Oxytocin, Eye Tracking, Social Impairments, Schizophrenia, Cognitive Function, Social Function, BACS, SFS

S185. Multisensory Integration in Long Term and First Episode Schizophrenia Spectrum

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Background: Long-term schizophrenia (Sz) and first episode schizophrenia spectrum (FE) individuals have deficits in processing auditory and visual stimuli, as evidenced by reduced event-related potentials. Multisensory integration (MSI) is the process by which streams of information from multiple modalities are integrated into a coherent percept. Findings from studies of non-linguistic MSI in Sz have been equivocal and no studies have assessed MSI in FE.
Methods: This study examined MSI by presenting 27 Sz and 23 matched (age, sex, IQ, pSES) healthy controls (HCSz), and 20 FE and 18 matched healthy controls (HCFE) with auditory (A), visual (V), and simultaneous audiovisual (AV) stimuli. Participants were asked to sit silently and pay attention to the stimuli presented. MSI was calculated by subtracting the sum of the unisensory stimuli from the simultaneous audiovisual stimulus [AV − (A+V)]. MSI amplitude was calculated as the average voltage between 95-115 ms for Sz and HCSz, 103-123 for FE and HCFE, and 173-193 ms for all groups at PO9 and PO10, similar to where previous studies have looked for MSI.
Results: MSI at 95-115 ms was reduced in Sz ($p=.020$), but not in FE at 103-123 ($p=.238$). MSI at 173-193 ms was not significantly different from controls for either Sz or FE.
Conclusions: These results suggest that early MSI is impaired in Sz but not FE, and may be related to disease progression or other secondary effects of chronicity.
Supported By: RO1 MH94328. National Institutes of Mental Health. Mismatch negativity and complex second-order sensory memory in schizophrenia
Keywords: Schizophrenia, Multisensory, EEG, Auditory Evoked Potential, Visual Evoked Potential

S186. Emotional Modulation of Target Detection in Deficit and Non-Deficit Schizophrenia

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Background: Emotional deficits are an integral feature of schizophrenia (SZ) but our understanding of these deficits is limited. In the present study, we sought to examine whether emotional deficits reflect difficulty in the cognitive processing of affective stimuli.
Methods: Healthy controls (HC; N=170) and stable outpatients with SZ (N=245), characterized as either deficit syndrome (DS; N=62) or non-deficit syndrome (NDS; N=183), completed an Affective Go/NoGo task requiring discrimination of positively, negatively or neutrally valenced words. Accuracy (d') and response bias (c) were calculated for each of the three conditions and a series of ANCOVAs were carried out to examine group differences.
Results: Examination of accuracy revealed significant main effects of group ($p<.001$) and valence ($p<.001$) and a significant Valence x Group interaction ($p=.04$) indicating that while emotional valence impacted accuracy for the HC and NDS groups, the DS group maintained the same low level of accuracy across all levels of emotional valences. Examination of response bias also revealed significant main effects of group ($p<.001$) and valence ($p<.001$) and a significant Valence x Group interaction ($p=.04$) such that he HC and NDS groups exhibited equivalent biases on negatively and positively

valenced words while response bias in the DS group was lowest for neutral, higher for negatively valenced and higher still for positively valenced words.
Conclusions: These results suggest that the severity of negative symptoms may be directly related to deficits in processing affective stimuli. Moreover, although this deficit is observed across both positively and negatively valenced stimuli, it is most pronounced for positive affective material.
Supported By: R00-MH086756; R01-MH079800
Keywords: Emotional Processing, Schizophrenia, Deficit Syndrome

S187. Hedonic Deficits in Schizophrenia and Major Depressive Disorder

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Background: Hedonic deficits have long been associated with schizophrenia (SZ) and major depressive disorder (MDD). Given the heterogeneity of these illnesses, however, as well as the substantial overlap in negative symptomatology and clinical presentation, our understanding of the precise mechanisms underlying these impairments remains poorly understood. Thus, the present study sought to examine hedonic deficits in SZ, MDD, and healthy control (HC) participants, and evaluate the predictors of these processes across groups.
Methods: Fifty-one patients with SZ, 43 patients with MDD, and 51 HCs were administered a battery of clinical and cognitive assessments. The Consummatory Pleasure subscale of the Temporal Experience of Pleasure Scale (TEPS) and the International Affective Picture Rating System (IAPS) were used to measure hedonic experience and hedonic capacity, respectively. Analyses of variance were used to assess for group differences. Hierarchical linear regressions were conducted to evaluate the predictive value of amotivation and depressive symptoms across the entire sample.
Results: There were no group differences in hedonic capacity; however, the MDD group endorsed significantly lower levels of hedonic experience compared to HCs ($p=.001$). Linear regression models revealed that clinical amotivation significantly predicted both TEPS-Con ($\beta=-.37$, $p<.001$) and IAPS ($\beta=-.29$, $p=.005$) pleasure ratings, above and beyond the effect of depressive symptoms.
Conclusions: Our results suggest that hedonic deficits in SZ and MDD are not driven by diagnostic status alone, but also by severity of clinical amotivation. Importantly, these findings underscore the distinctions between hedonic capacity, hedonic experience, and depressive symptoms, and highlight the role of motivation underlying hedonic processes across disorders.
Supported By: OMHF
Keywords: Schizophrenia, Major Depressive Disorder (MDD), Amotivation, Hedonic Capacity, Hedonic Experience

S188. Emotional processing in Bipolar Disorder With and Without Psychosis: Findings From the Psychosis and Affective Research Domains and Intermediate Phenotypes Consortium

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Background: Approximately half of bipolar I disorder (BD) cases manifest with psychosis. Studies have reported abnormal electrophysiological (EEG) responses to emotional stimuli in BD, however no previous EEG research has examined these differences between psychotic (BDP) and non-psychotic BD (BDN) in a large well-characterized sample. The present study examined neural emotional processing in BDP and BDN to determine if psychosis affects neural responses to affective stimuli.
Methods: 348 individuals (HC=172, BDP=110, BDN=66) from the 3-site PARDIP consortium viewed neutral, pleasant, and unpleasant images from the International Affective Picture System (IAPS) while EEG was recorded. Using a spatial PCA, two event-related potential (ERP) components were identified at early (150-250 ms) and late (400-900 ms) time periods. Group by image category ANOVAs were completed for each component. Follow up ANOVAs were completed as appropriate.
Results: Early and late ERPs were modulated by emotional content in all participant groups. Amplitude differed slightly between pleasant and unpleasant images, with significant variation between picture subtypes. Early and late amplitudes did not differ between healthy, BDP, and BDN groups for any picture category [$F(2, 345)=.78$, $p=.46$), $F(2, 345)=.11$, $p=.90$, $F(2, 345)=1.17$, $p=.31$, $F(2, 345)=.31$, $p=.74$].
Conclusions: This study was unable to replicate previous findings of abnormal EEG responses to emotional stimuli in BD and found no effect of psychosis, suggesting that BD has intact bottom-up and associative neural processing of emotional stimuli. These results raise questions regarding the utility of this measure for indexing BD and psychosis-related dysregulation, but further analysis of latency effects and neurobiological psychosis categorizations is necessary.
Supported By: Multiple RO1s: MH096913, MH096957, MH096900, MH096942, MH077851, MH077945, MH103368, MH078113, MH103366
Keywords: Psychotic Disorders, Bipolar Disorders, Emotional Processing, Event Related Potentials

S189. Lower- and Higher-Level Factors of Social Cognition Relate to Neurocognition and Functional Outcome Across Schizophrenia Spectrum Disorders and Healthy Controls

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Background: Schizophrenia spectrum disorders (SSDs) often feature social cognitive deficits. However, little work has focused on the structure of social cognition, and results have been inconsistent in schizophrenia. Our objective was to elucidate the factor structure of social cognition across individuals with SSDs and healthy controls. We hypothesized that a two-factor model, including lower-level "simulation" and higher-level "mentalizing" factors, would demonstrate the best fit across participants.
Methods: 164 participants with SSDs and 102 healthy controls completed social cognitive tasks ranging from emotion recognition to complex mental state inference, as well as clinical, functional outcome, and neurocognitive measures. Confirmatory factor analyses (CFAs) were conducted to test social cognitive models, models of social cognition and neurocognition, and measurement invariance between patients and controls.
Results: A two-factor (simulation, mentalizing) model fit the social cognitive data best (RMSEA=0.00, CFI=1.00), and multi-group CFAs demonstrated adequate measurement invariance, across patients and controls. Patients showed lower simulation and mentalizing factor scores than controls ($p<.001$), and scores on both factors correlated with clinical and functional outcome measures. Including neurocognitive data, a higher-order two-factor (social cognition, neurocognition) model fit the data well (RMSEA=.046, CFI=.971), and social cognition mediated the relationship between neurocognition and functional outcome ($p<.05$).
Conclusions: Our results support distinguishing lower- and higher-level social cognition across individuals with SSDs and healthy controls, and suggest that they may have partially distinct underlying mechanisms. Further, they confirm the importance of social cognition with regard to clinical and functional outcomes, and thereby as a potential treatment target in SSDs.
Supported By: NIMH R01MH102324, R01MH102313, R01MH102318; CAMH Postdoctoral Fellowship
Keywords: Schizophrenia, Social Cognition, Neurocognition, Functional Outcome

S190. Prevention of Relapse in Schizophrenia: A Phase II Study Evaluating Efficacy, Safety, and Tolerability of Oral BI 409306

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Background: Currently, no drugs are approved for the prevention of relapse in schizophrenia. Here we describe a study of BI 409306, a phosphodiesterase-9 inhibitor, in the prevention of relapse in schizophrenia.
Methods: A proof-of-concept study investigating the efficacy, safety, and tolerability of BI 409306 versus placebo is planned.
Results: During this multinational, double-blind, parallel-group study, patients (aged 18–55 years) with schizophrenia, receiving stable antipsychotic medication for ≥12 weeks, with a Clinical Global Impression-Severity (CGI-S) score ≤4 and a Positive and Negative Syndrome Scale (PANSS) score ≤80 (and ≤4 on conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) will be eligible if they have experienced ≥2 relapses within the past 5 years (or ≥1 relapse if diagnosed <3 years ago). Overall, 387 patients are planned for randomization (1:1:1) to oral BI 409306 25 mg, 50 mg, or placebo, once-daily for 28 weeks (4-week follow-up).

Relapse will be defined as hospitalization, intensive outpatient therapy, or increased intensity of home treatment, predefined questionnaire responses on the CGI-S, PANSS, or Columbia Suicide Severity Rating Scale (C-SSRS), a new prescription or increased dose of antipsychotic medication, or suicidal or homicidal ideation or behavior. Secondary endpoints: change from baseline in PANSS positive symptom score, CGI-S and Patient Global Impression of Improvement (PGI-I); change in antipsychotic medication; reduction in serious adverse events (SAEs); suicidal behavior/ideation (C-SSRS); and time to relapse. Safety will be assessed throughout.
Conclusions: This study will test a novel drug mechanism in the prevention of relapse in schizophrenia.
Supported By: Boehringer Ingelheim (1289.49)
Keywords: Clinical Trials, Efficacy, Phosphodiesterase 9 Inhibitor, Relapse, Schizophrenia

S191. The Odor of the Real Walking Dead: Co-occurrence of Cotards and Olfactory Reference Syndromes

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Background: The co-occurrence of Cotard's syndrome, the delusion of being fully or partially dead (Debruyne, 2009), and Olfactory Reference Syndrome, the belief that an odor is emanating from the sufferer (Hirsch, 2015), has not heretofore been described. Such a case is presented.
Methods: Case study: A 35 year-old right-handed female presented with the belief that she had died and was putrefying from the inside-out. She would intensely valsalva to eliminate her internal decaying corpus, inducing a hernia. She feared her miasmic flatulence would kill her roommate since the mephitic gas was emanating from her anus. She perceived a ghastly aroma of trash from her bowels, and was paranoid believing that others were laughing and talking about her disparagingly, that she literally possessed the air of trash. Fearing such a release, she would avoid bowel movements and suffered from chronic constipation. Metallic phantogeusia also appeared when the patient did not have a bowel movement for a prolonged period of time.
Results: Her symptoms have been unresponsive to duloxetine, quetiapine, risperidone, ziprasidone, haloperidol, bisacodyl, docusate, and lactulose.

Conclusions: The somatoform delusion of Cotard's Syndrome of being dead and putrefying fecal matter obstructing the intestine, served as a nidus for the nosopoetic Olfactory Reference Syndrome delusion (Lochner, 2003). While initially a full Cotards syndrome with the entire body being dead, over time the psychosis consolidated to decomposing bowels. Query as to Cotards and Olfactory Reference Syndrome in those with complaints of chronic constipation may be revealing, and may aid in approaches for this condition.
Keywords: Cotard's Delusions, Aroma, Olfactory Reference, Bowels, Psychosis

S192. Effects of Transcranial Stimulation on Cognition and Brain Functional Changes in Schizophrenia

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Background: Transcranial direct current stimulation (tDCS) has been reported to improve cognition and symptoms in schizophrenia. The brain mechanisms underlying these effects have not been systematically explored. We report a double-blind study which measured effects of tDCS on cognition, symptoms, and brain activation in schizophrenia.
Methods: 41 Chinese schizophrenics were randomized to receive 10 sessions of Active or Sham tDCS. Cognition was evaluated with the MATRICS(MCCB), Paced Auditory Serial Addition Task and CogState. Psychiatric symptoms were evaluated with PANSS. Brain function were evaluated with fMRI at baseline and after 10 tDCS sessions for resting state changes in brain activation.
Results: There were no strong effects ($P<.05$) of Active vs Sham tDCS on cognition, but there were significant ($P<.01$) effects on differences in brain activation assessed by fMRI. On MCCB, there were trends ($P=.06$) for Active tDCS vs. Sham tDCS to improve Speed of Processing. There were no effects of active vs sham tDCS on psychiatric symptoms. There were significant differences between active vs sham tDCS on resting state activation in several brain areas including middle frontal gyrus, superior frontal gyrus and superior and inferior parietal gyrus; active tDCS increased and sham tDCS decreased activation. There were significant relationships between changes in several MCCB scores and changes in brain activation in specific areas.
Conclusions: tDCS had significant effects on resting state brain activation which were significantly related to changes in MCCB. However, in this sample 10 sessions of active vs sham tDCS did not show marked effects on overall cognitive function.
Keywords: Transcranial Direct Current Stimulation (tDCS), Brain Imaging, fMRI, Cognitive Performance, Schizophrenia, MATRICS

S193. Brain Variability in Schizophrenia Spectrum Disorder

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Background: Accumulating evidence converges on a characteristic pattern of lower fronto-temporal cortical thickness in patients with schizophrenia (SZ) compared to controls. However, SZ is a heterogeneous disorder, and conventional mean-based analyses may disguise a substantial heterogeneity among patients. A recent meta-analysis reported higher brain volume variability in SZ patients in several cortical and subcortical structures lower variability in anterior cingulate volume as compared to healthy taken to indicate a pervasive involvement of the anterior cingulate in SZ. Here, we compared regional brain structural dispersion within patients with SZ and controls using a mega-analytic approach.
Methods: T1-images from 1254 patients and 2066 controls from 15 cohorts were processed using Freesurfer (5.3.0). Cortical thickness, area and volume maps were submitted to vertex-wise analysis using double generalised linear models in R, yielding vertex-wise case-control dispersion maps. Scanner-effects were regressed out by fitting generalized additive models. The dispersion model was fitted to the residuals after modelling the mean effect of age, sex and diagnosis on the scanner-residualized vertex-wise values, and included age and sex as covariates. The statistical maps were corrected using FDR ($q=.05$).
Results: The deviance models revealed significantly higher dispersion in cortical thickness in patients in fronto-parietal and temporal regions.
Conclusions: Higher variability in cortical thickness within the patient group support that SZ is a heterogeneous disorder, possibly comprising sub-groups with distinct pathophysiology. Further studies assessing the origin and correlates of this substantial variability are needed to

delineate and fractionate the pathophysiological mechanisms of SZ spectrum disorders.
Supported By: Research Council of Norway, South-Eastern Norway Regional Health Authority, KG Jebsen Foundation, European Commission 7th Framework Programme
Keywords: Schizophrenia, Cognitive Function, Social Function, BACS, SFS, Surface-Based Morphometry, Brain Structural Variability

S194. Reduced Serum Brain-Derived Neurotrophic Factor Associated With Later Clinical Illness Stages of Psychosis Continuum Disorder

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Background: Several studies have found reduced serum BDNF in severe mental disorders, but sample sizes have been low with variation in BDNF measure methodology and heterogeneity in study samples. Here, we aimed to clarify the role of serum BDNF in patients with a psychosis continuum disorder, and the relationship to clinical illness staging, current remission status, and childhood trauma.
Methods: The study comprised of 1484 individuals (schizophrenia; SZ [n=589], bipolar disorder, BD [n=254]), major depressive disorder, MDD [n=38], and healthy controls, HC [n=603]). BDNF was measured in serum. Childhood trauma events were collected using the Childhood Trauma Questionnaire (CTQ). Clinical illness stage was measured by numbers of episodes and calculated based on Diagnostic and Statistical Manual of Mental Disorders (DSM).
Results: Patients with SZ, BD, or MDD had lower serum BDNF than the HC group (p=0.001, p=0.001, p=0.01, respectively). No significant differences in serum BDNF levels were observed within the patient group. Within the patient sample, reduced serum BDNF was associated with more depressive (p=0.04) and psychotic episodes (p=0.04). Patients reporting childhood sexual abuse had more affective (p=0.01) and non-affective episodes (p=0.02), and lower serum BDNF levels (p=0.04). Longer time in remission was associated with higher serum BDNF levels (p=0.02).
Conclusions: Reduced BDNF was found across diagnoses of SZ, BD, and MDD, with the most substantial reduction in patients reporting childhood sexual abuse experiences. Secondly, our study supports reduced serum BDNF levels as a marker of illness severity with lower levels indicating more severe illness, characterized by more affective and non-affective episodes.
Supported By: Narsad Young Investigator Award to Monica Aas (#22388). South-Eastern Norway Health Authority (#2017060, #2013088), the Research Council of Norway, the KG Jebsen Stiftelsen
Keywords: Schizophrenia, Bipolar Disorder, Depression, Childhood Trauma, BDNF

S195. Processing Speed and Negative Symptoms Predict Functional Outcomes Assessed in Later Years in Japanese Patients With Schizophrenia

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Background: Longitudinal studies of patients with schizophrenia showed mixed results regarding the trajectory of cognitive impairment, while cross-sectional studies showed that cognitive impairment and severity of negative symptoms are robust predictors of poor social functioning. We aimed to investigate whether cognitive performance and clinical variables predict the functional outcome assessed years later.
Methods: 86 patients with chronic schizophrenia (42.7±10.1 years old at enrollment) and age- and sex-matched 55 healthy controls (40.3±10.4 years old at enrollment) were recruited. Both of patients and controls were assessed by the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS) at the enrollment and 7 years later (2nd assessment). The patients were also assessed by the Social Functioning Scale (SFS) at the second assessment.
Results: The intra-group comparison using paired-t tests revealed that controls had a significant improvement in verbal memory, digit sequence task and token motor task z-scores and composite scores at the second assessment, while patients with schizophrenia did so only in verbal memory z-scores. The Structural Equation Modeling revealed that the lesser negative symptoms, better performance on BACS composite score (or BACS symbol coding z-score in selecting all of the z-scores from six BACS domains) and higher age at onset of the disease predicted the higher total SFS score at the second assessment.
Conclusions: These results suggest that cognitive performance, except for verbal memory, is stable in patients with chronic schizophrenia during the course of disease, and that the processing speed and negative symptoms predict the degree of functioning assessed seven years later.
Keywords: Cognitive Dysfunction, Schizophrenia, Social Functioning, BACS, Negative Symptoms

S196. Evidence for 'Unstable Attractor' Dynamics in Inference in Schizophrenia

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Background: Subjects with a diagnosis of schizophrenia (Scz) overweight unexpected evidence in probabilistic inference. A neurobiological explanation for this effect is that cortical disinhibition (e.g. hypofunction of interneuron N-methyl-D-aspartate receptors) in Scz makes neural network states (or 'attractors') unstable and easily altered: in predictive coding,

this means reduced precision of prior beliefs. Indeed, previous work modelling EEG data in the mismatch negativity (an archetypal predictive coding paradigm) showed prefrontal disinhibition in both Scz and their relatives.
Methods: Hierarchical Bayesian belief updating models were tested in two independent datasets (n=80 − published previously − and n=167) comprising subjects with schizophrenia, and both clinical and non-clinical controls (some tested when unwell and on recovery) performing the 'probability estimates' version of the beads task (a probabilistic inference task). Models with a standard learning rate or including a parameter encoding the effects of attractor instability were formally compared.
Results: The model simulating unstable attractors had most evidence in all groups in both datasets. Two of its four parameters differed between Scz and non-clinical controls in each dataset: attractor instability (p=0.01 and p=0.00004 in datasets 1 and 2) and response stochasticity (p=0.002, p=0.0007). These parameters correlated in both datasets (ρ=-0.38, p=0.0004; ρ=-0.35, p=0.000001). The clinical controls showed similar parameter distributions to Scz when unwell, but were no different to controls once recovered.
Conclusions: These findings support the hypothesis that attractor network instability - or in predictive coding terms, greater prior variance - contributes to belief updating abnormalities in Scz, and raise questions about potential glutamatergic or other neuromodulatory mechanisms.
Supported By: Academy of Medical Sciences (AMS-SGCL13-Adams), National Institute of Health Research
Keywords: Schizophrenia, Computational Psychiatry, Bayesian Model

S197. Self-Assessment of Social Cognitive Ability in Schizophrenia: Association With Social Cognitive Test Performance, Informant Assessments of Social Cognitive Ability, and Everyday Outcomes

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Background: Impairments in self-assessment of abilities are commonly found in people with schizophrenia and impairments in introspective accuracy (IA) have been found to predict impaired functional outcome. We examined IA of social cognitive ability and related assessments of social cognition provided by informants, to performance on tests of social cognitive ability, and to everyday outcomes rated by informants. The difference between self-reported social cognitive abilities and informant ratings was our measure of IA.
Methods: People with schizophrenia (n=135) performed 8 different tests of social cognitive abilities. They rated their social cognitive abilities on the Observable Social Cognition Rating Scale (OSCARs). High contact informants also rated social cognitive ability and everyday outcomes, while unaware of the patients' performance and self-assessments. Also measured were social competence with a performance-based assessment and clinical ratings of negative symptoms.
Results: Patient reports of their social cognitive abilities were uncorrelated with performance on social cognitive tests and with three of the four domains of everyday functional outcomes rated by informants. IA, in specific overestimation of performance, predicted impaired everyday functioning across all four functional domains. IA scores predicted functional outcomes even when the influences of social cognitive performance, social competence, and negative symptoms were considered in regression models.
Conclusions: Mis-estimation of social cognitive ability was a more important predictor of social and nonsocial outcomes in schizophrenia than performance on social cognitive tests. These results suggest that consideration of IA is critical both when attempting to assess causes of everyday disability and when trying to implement interventions aimed at disability reduction.
Supported By: NIMH 93432
Keywords: Schizophrenia, Social Cognition, Metacognition

S198. Preliminary Analysis of Selective Attention Deficits in First-Episode Schizophrenia

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Background: Little is known about the biological mechanisms related to deficits in modulation by selective attention of sensory processing in schizophrenia, nor such pathophysiology early in disease course. To that end, we examined N2pc, a brainwave related to visual selective attention, at first psychotic episode.
Methods: Thirty-six first-episode schizophrenia spectrum (FESz) and 27 healthy control (HC) individuals completed two target detection tasks that required different degrees of top-down attentional control, pop-out and serial visual search. The N2pc was measured at occipito-parietal electrode sites.
Results: FESz exhibited reduced N2pc ($p < 0.05$) at PO3/PO4 across tasks. In HC larger pop-out N2pc was marginally associated with shorter RT ($r = .35$, $p = .07$), and larger visual search N2pc was associated with better accuracy ($r = -.52$, $p = 006$). By contrast, in FESz larger pop-out N2pc was associated with better accuracy ($r = -.57$, $p < .001$), but larger visual search N2pc was not associated with RT or accuracy.
Conclusions: Reductions in the N2pc in FESz indicate an impaired ability to modulate sensory input via selective attention, whether largely bottom-up or top-down. In HC the ability to modulate visual signals, as reflected in N2pc, was associated with faster RT for the bottom-up task and improved accuracy for the top-down task. Larger N2pc impacted pop-out accuracy for FESz, but was not associated with serial search performance. These results suggest that even at first break, task performance that should be largely bottom-up (pop-out) necessitates greater top-down control, with little resources available for tasks that require great cognitive control (serial search).

Supported By: NIH P50 MH103204
Keywords: First Episode Psychosis, Attentional Control, Electroencephalography (EEG), Pop-Out/Visual Search

S199. Predictive Coding During an Oddball Task in Schizophrenia and the Psychosis Risk Syndrome

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Background: The P300 event-related potential (ERP) component is typically elicited during an oddball task by infrequent target or novel deviant stimuli (P3b and P3a subcomponents, respectively) that are randomly interspersed among frequent standard stimuli. Standard stimuli can also elicit a P300 if they are relatively unlikely to occur within local sequences of standards, as the implicit context created by local stimulus probabilities can render standard stimuli improbable and therefore, deviant. Previously, we showed that healthy individuals generate a P3a in response to low probability standards, yet chronic schizophrenia patients failed to generate this response. The present study examined P3a associated with standard stimuli in young patients with early illness schizophrenia (YSZ) and in individuals at clinical high risk for psychosis (CHR).
Methods: ERPs were recorded from 43 CHR, 19 YSZ, and 43 healthy comparison (HC) participants during a visual oddball task containing frequent (80%) standard stimuli and infrequent deviant stimuli.
Results: A standard position effect ($p<.001$), indicating that lower probability standard stimuli elicited a larger P3a, was qualified by a group x standard position interaction ($p=.01$). Linear contrasts demonstrated a greater increase in P3a amplitudes to lower probability standards in both HC and CHR relative to YSZ.
Conclusions: Results provide further evidence that standard stimuli in an oddball sequence can be rendered implicitly deviant based on their sequential improbability. Furthermore, the previously observed failure of chronic schizophrenia patients to implicitly process local sequential stimulus probabilities was evident in YSZ but not CHR, consistent with the emergence of deficient task-based predictive coding with schizophrenia onset.
Supported By: VA Office of Academic Affiliations Advanced Fellowship in Mental Illness Research and Treatment; NIMH
Keywords: Schizophrenia, Clinical High Risk for Psychosis, P300, Event-Related Potentials, Predictive Coding

S200. The Association Between Neural Activation During a Simple Response Conflict Task and Antipsychotic Treatment Response in First-Episode Psychosis

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Background: Psychosis is associated with dysregulation of frontal lobe functioning, but whether hypo- or hyper-activation is present remains a contentious issue. Moreover, there is a critical need to identify simple neuroimaging biomarkers for predicting antipsychotic treatment response in psychosis. In the present study, we examined task-based brain activation in first-episode psychosis during a simple response conflict task, and correlated brain activation at the onset of treatment with clinical response 12 weeks later.
Methods: BOLD fMRI data were collected while patients experiencing their first psychotic episode ($n=40$) and healthy volunteers ($n=33$) completed a task in which they pressed a response button corresponding to the same side or opposite side of a circle that appeared to the right or left of central fixation. BOLD data were analyzed using ANCOVA with symptom severity (BPRS scores) and cognitive task performance as regressors. Results were corrected for multiple comparisons.
Results: For the contrast of opposite-side vs. same-side, patients showed significantly greater activation compared with healthy volunteers in anterior cingulate cortex and intraparietal sulcus. Among patients, there was an association between BPRS scores and activation in ventrolateral PFC. Additionally, greater anterior cingulate cortex, temporal-parietal junction, and superior temporal cortex activation predicted greater symptom reduction and therapeutic response following treatment ($p<.05$, corrected).
Conclusions: Intact performance on this parsimonious task was associated with frontal hyperactivity suggesting the need for patients to utilize greater neural resources to achieve task performance comparable to healthy individuals. Moreover, activation observed using a simple fMRI task may provide a biomarker for predicting treatment response in first-episode psychosis.
Supported By: RO1MH076995; M01RR018535; P30MH090590; P50MH080173; Hofstra University
Keywords: First Episode Psychosis, Functional Magnetic Resonance Imaging, Executive Function, Treatment Response, Anterior Cingulate Cortex

S201. Correlates of Neurocognitive Functions in Patients With At-Risk Mental State: A 6-Month Follow-Up Study

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Background: Cognitive deficits are evident at the prodromal phase of psychosis. It has been noted that brain-derived neurotrophic factor (BDNF) is correlated with cognition in both preclinical and clinical studies. However, to our knowledge, no

study has evaluated blood BDNF levels and their association with cognitive impairment in patients with at-risk mental state (ARMS).
Methods: We included 13 patients with ARMS and 30 healthy controls (HC) matched by sex, age, and educational level. Plasma BDNF levels were measured in patients at baseline and six months, and in HC at baseline. Neurocognitive functions (executive functions, speed of processing, verbal learning and memory, working memory) were examined in the patients at 6 months, and in HC at baseline. Regression analyses were conducted to examine the relationship between BDNF levels and cognitive performance.
Results: BDNF levels were lower in ARMS group than in HC group both at baseline and at 6 months ($p=0.001$, $p=0.008$, respectively). ARMS group showed lower scores in global cognition, speed of processing, and verbal learning and memory compared with HC group ($p=0.002$, $p=0.001$, $p=0.005$, respectively). There were no associations between plasma BDNF levels and all of the cognitive domains in both groups.
Conclusions: Peripheral BDNF levels were not related to cognitive deficits in ARMS and HC groups while the lower BDNF level in the former persisted up to 6 months. Further research is needed in a large sample.
Keywords: Brain-Derived Neurotrophic Factor, Cognitive Function, Prodromal Psychosis, At-Risk Mental States

S202. Event-Related Repetitive TMS to Right Posterior STS (but not OFA) in Healthy Volunteers (HV) Briefly Recapitulates Face Emotion Recognition (FER) Deficits of Schizophrenia

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Background: Profound FER deficits exist in Sz, causing social disability, though can be partly remediated with computer-based training. Neurostimulation might augment remediation if critical nodes were identified. We aimed to 1) briefly recapitulate FER deficits of Sz in HV using rTMS to rpSTS, 2) identify connectivity patterns of rpSTS regressed by FER, and 3) apply TMS to rpSTS with fMRI as readout.
Methods: 1) Nine healthy volunteers had rTMS (10 Hz; 500 msec; 110% RMT) to rpSTS or rOFA (counterbalanced; 10/10 system overlay with standard MRI) concurrent (1/3 trials) with stimuli (http://faces.mpdl.mpg.de/) for emotion or gender identification (button press). 14 Sz patients completed these tasks without TMS. 2) Whole-brain resting-connectivity analyses, seeded by rpSTS, was applied in 27 Sz and 35 HV who also completed the UPenn FER task. 3) BOLD fMRI was obtained in 4 HV pre- and post-TMS to rpSTS (1 Hz; 20 minutes).
Results: 1) In HV, rTMS to rpSTS only (not OFA) significantly slowed reaction time for FER only (not gender identification): overall F test for logRT ($p=.001$) with post-hoc rpSTS vs.OFA ($p=.005$) and rpSTS vs. non-stim trials ($p=.004$). rpSTS recapitulated slowed RT ad lower FER accuracy of Sz. 2) In both HV and Sz, rpSTS had significant resting connectivity with V1 ($p= .00013$), positively modulated by FER accuracy. 3) Analyses are ongoing.
Conclusions: rpSTS is a critical node in the FER circuit with connectivity to primary visual cortex modulated by FER, whose disruption recapitulates FER deficits, making it a candidate target for remediatory neurostimulation.
Supported By: NYS OMH, Columbia and NYS pilot imaging awards
Keywords: Transcranial Magnetic Stimulation, Schizophrenia, Emotional Face Processing, Superior Temporal Gyrus, Resting State fMRI

S203. Impact of Schizophrenia on Temporal Context Versus Item Memory

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Background: Bridging temporal gaps are a core feature of episodic memory, allowing for "mental time travel" and a sense of recollection. Given evidence of disproportionate recollection versus familiarity deficits, we hypothesized that patients would have differential memory impairments for temporal versus item information.
Methods: 41 first episode schizophrenia patients and 43 healthy controls completed two tasks; 1) Temporal Order Working Memory (TO_WM), which requires individuals to maintain information about a set of 4 fractal images to respond to either item probes (old/new recognition) or temporal order probes (which was seen first?) after a 3 second delay. 2) Temporal Sequence Learning task (TS_Learn), which trains participants on a set of fixed, random, or novel sequences of visual objects. During retrieval, a continuous list - including embedded sequences, is presented, and participants quickly respond to a semantic probe on each item. Sequence learning is demonstrated by faster reaction times (RT) for fixed versus random sequences. Repeated-measures analyses of variance (ANOVA) were performed to test for group by condition interactions, which would support study hypothesis.
Results: As predicted, TO_WM showed a group by condition interaction [$F(1,70) = 5.89$, $p<0.05$], with patients showing disproportionate memory impairments for temporal order versus item information. A similar interaction was also observed for TS_Learn, [$F(1,66) = 4.87$, $p<0.05$], with attenuation of the RT facilitation effect for fixed versus random sequences in the patient sample.
Conclusions: Patients appear to have greater difficulty remembering temporal versus item information, suggesting that their disproportionate recollection deficits may relate to difficulty utilizing temporal context during memory formation.
Supported By: NIH R01MH105411
Keywords: Episodic Memory, Context, Early Psychosis

S204. Duration of Untreated Psychosis, Working Memory Activation, and Frontostriatal Connectivity in Patients With First-Episode Psychosis

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Background: A longer duration of untreated psychosis (DUP) has been linked with worsened response to antipsychotic treatment and variation in corticostriatal functional connectivity within the central executive network. The following study examined the link between DUP and working memory (WM) activation, as well as task-related background functional connectivity within corticostriatal nodes in patients with first-episode psychosis (FEP).
Methods: Patients with FEP (N=39) underwent fMRI scanning while performing a visual WM task. We examined relationships between duration of psychosis and (1) magnitude of engagement of frontostriatal regions and (2) strength of functional coupling between prefrontal and striatal regions. Task activation was examined within the striatum and a priori regions of interest (ROIs) in the prefrontal cortex determined by prior studies of visual WM activation via Neurosynth (Yarkoni et al. 2011). An analysis of background functional connectivity between our prefrontal ROIs and striatal regions was performed on spontaneous residual fluctuations, following removal of task-evoked activation.
Results: During WM activation, longer DUP was associated with greater engagement of left dorsolateral prefrontal cortex during WM maintenance with low load, but less engagement with higher load. The connectivity analysis showed that longer DUP was associated with greater functional coupling between striatum and the anterior cingulate, bilaterally, and the dorsolateral prefrontal cortex. Results were not related to performance or reaction time.
Conclusions: These results provide confirmatory evidence for a link between corticostriatal interactions and DUP. In addition, these findings advance our understanding of a compensatory neural mechanism that may underlie the negative relationship between poor clinical outcomes and longer DUP.
Supported By: NIH (P50MH103204)
Keywords: First Episode Psychosis (FEP), Functional Connectivity, Striatum, Working Memory

S205. Hierarchical Bayesian Modeling of Abnormal Eye Gaze Perception in Schizophrenia and Bipolar Disorder: Self-Referential Tendency, Perceptual Sensitivity, and Sex Differences

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Background: Eye gaze perception is a foundation of social cognition and determinant of functional outcome in severe mental illnesses. Previous studies suggest abnormal gaze perception in schizophrenia (SZ) and bipolar disorder (BD). This study used psychophysics methods to quantify deficits at the perceptual and interpretation levels, and hierarchical Bayesian modeling to derive more accurate and valid estimates of these deficits.
Methods: The sample consisted of 156 participants, including 47 SZ (34% female; age = 41.4 ± 14.4), 55 BP (69% female; age = 37.6 ± 11.5), and 54 healthy controls (HC) (39% female; age = 36.7 ± 13.0). They viewed faces with varying gaze directions and made two-forced choice eye-contact judgments. Responses were modeled to follow a binomial distribution and estimated using a logit link function. Absolute threshold and slope of the logistic function were used to index self-referential tendency and visual perception sensitivity, respectively. Markov Chain Monte Carlo (MCMC) was used to sample from the joint posterior distribution of the (hyper)parameters.
Results: Both clinical groups showed high posterior probabilities of self-referential bias (SZ: 98.7%; BP: 93.71%) and reduced perceptual sensitivity (SZ: 99.96%; BP: 98.7%) compared with HC. Male and female patients showed similar degrees of self-referential bias, but the magnitude of reduced perceptual sensitivity in men was more than twice as in women.
Conclusions: The results suggest that altered social cognition in both SZ and BP is characterized by abnormal cognition at both the perceptual and interpretation levels, and the degree of deficits is dependent on sex.
Supported By: K23 MH108823
Keywords: Social Cognition, Psychophysics, Bayesian Model, Schizophrenia, Bipolar Disorder

S206. Cerebellar Transcranial Direct Current Stimulation (tDCS) Improves Procedural Learning in Non-Clinical Psychosis

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Background: Literature suggests that cerebellar dysfunction may contribute to motor learning deficits characteristic of psychosis. Transcranial direct current stimulation (tDCS) may provide a non-invasive way of normalizing cerebellar function. While studies targeting other brain regions with tDCS (e.g. dorsal lateral prefrontal cortex) have observed improvements in both symptomatology and cognition among patients with schizophrenia, to date there have been no investigations examining cerebellar stimulation or procedural learning in a psychosis or psychosis risk population. The present double-blind crossover study examines the effects of cerebellar tDCS in controls and in an analogue population to psychosis: individuals reporting elevated symptoms of non-clinical psychosis (NCP).
Methods: A total of 18 controls and 24 NCP individuals were randomized into conditions consisting of 25 minutes of anodal cerebellar tDCS or sham stimulation. Following this, both groups completed a pursuit rotor task designed to measure

procedural learning performance. Participants then returned one-week later and received the corresponding condition (either anodal stimulation or sham) and repeated the pursuit rotor task.
Results: Results indicate that in the sham condition, control participants showed significantly greater rates of motor learning across trials when compared with the NCP group. In the anodal cerebellar tDCS stimulation condition, the NCP group exhibited significant improvements in the rate of motor learning and performed at a level that was comparable to controls; these data support the link between cerebellar dysfunction and motor learning.
Conclusions: Taken together, tDCS may be a promising treatment mechanism for patient populations and a useful experimental approach in elucidating our understanding of psychosis.
Supported By: NARSAD
Keywords: Brain Stimulation, Cerebellum, Cognition, Learning, Psychosis-Proneness

S207. Antipsychotics-Induced Extrapyramidal Symptoms Associated Functional Connectivity Derived From Bivariate Analysis of Coherence and Phase Locking Value in Patients With Schizophrenia

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Background: Extrapyramidal side effects (EPS) are accompanied by motor, emotional, and cognitive symptoms which are the subject of functional connectivity among brain regions.
Methods: Twenty-eight patients with schizophrenia under antipsychotics were recruited. Coherence (COH) and phase locking value (PLV) were calculated with Neurophysiological Biomarker Toolbox from qEEG acquired in the resting state and averaged from electrode channels in designated brain regions, frontal (F), temporal (T), central (C), and occipitoparietal (OP). EPS were evaluated with clinician-rating drug-induced extrapyramidal symptoms scale (DIEPSS) and self-reported Liverpool university neuroleptic side effect rating scale (LUNSERS).
Results: In COH, chlorpromazine equivalent dose (CPZ-eq) showed significant correlation of functional connectivity with F-T, F-C, T-OP, T-C, C-OP in delta band, DIEPSS showed negative correlation with F-C gamma, LUNSERS showed positive correlations with C-OP beta, T-OP theta, and F-C alpha. Although correlations among LUNSRES, Red-herring and LUNSERS-psychic side effects (PSY) were highly strong, Red-herring did not show any correlation but LUNSER-PSY showed correlations with F-T and T-C in theta and alpha bands, F-C in delta and alpha bands, and T-OP in theta, alpha, beta bands. In PLV, CPZ-eq showed correlations with F-T and T-OP in delta, LUNSERS with C-OP in gamma, DIEPSS showed negative correlation only with T-OP in theta and LUNSERS-PSY with C-OP and T-OP in alpha, beta and gamma bands. LUNSERS seemed to have more correlations in all bands than DIEPSS.
Conclusions: COH and PLV could be useful to estimate CPZ-eq and to investigate pathophysiology of self-reported psychic side effects, a major cause of non-compliance with antipsychotics.
Supported By: The National Research Foundation of Korea (NRF)
Keywords: Schizophrenia, Antipsychotics, Functional Connectivity, Quantitative Electroencephalography (qEEG), EPS

S208. Incidence of Psychosis Related to Isoniazid: A Retrospective Descriptive Study

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Background: Isoniazid is a primary medication in the treatment of active and latent tuberculosis (TB). It has been associated with psychiatric complications such as hallucinations, delusions, anxiety, and insomnia. However, there are no large studies evaluating the incidence of psychiatric outcomes in patients taking isoniazid. In this study, we assessed the incidence of psychosis, the most debilitating adverse psychiatric event associated with isoniazid administration.
Methods: We searched all Mayo Clinic patients over age 18 with research authorization between January 1, 1987 and August 1, 2017 for those who were prescribed isoniazid. We subsequently performed chart reviews on included patients with one or more of the following terms in any clinical note: psychosis, hallucination, delusion, paranoia or mania. Two investigators determined whether there was an association between isoniazid utilization and psychotic symptoms.
Results: A total of 2511 patients were prescribed isoniazid. 89 patients had psychotic symptoms at any time. 33 patients had psychotic symptoms during isoniazid therapy. When other causative factors for psychosis were ruled out, 23 patients (0.9%; average age: 46, range 18-68; 10 female) had psychosis potentially related to isoniazid use. Of the 23, 14 (60.9%) had prior diagnoses of psychiatric illnesses.
Conclusions: In a large sample of patients taking isoniazid, the incidence of probable drug-related psychosis was 0.9%. This is slightly lower than a previously reported rate of isoniazid-induced psychosis of 1.6% but substantially higher than the average yearly incidence of psychosis in the general population of 0.01-0.015%. Physicians should be aware of this possible psychiatric adverse event in patients taking isoniazid.
Keywords: Side Effects, Clinical High-Risk States for Psychosis, Epidemiology

S209. Genome-Wide Association of Endophenotypes for Schizophrenia From the Consortium On the Genetics of Schizophrenia (COGS) Study

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Background: We have previously reported our efforts to characterize the genetic architecture of 12 heritable endophenotypes for schizophrenia in the COGS-1 family sample. Candidate gene association and genome-wide linkage results converge on a single network related to glutamate signaling. We now report genome-wide association results for these endophenotypes in an independent cohort of schizophrenia cases and controls.
Methods: PsychChip genotypes were obtained for 1729 subjects. Through the PGC pipeline, we applied standard quality control filters, confirmed ancestry, and imputed >6M variants with a genotyping rate >0.99. The final dataset included 1,533 subjects of European or Latino ancestry. Association was performed using linear regression and adjusting for age, sex, and five principal components. Results were combined through weighted meta-analysis.
Results: Analyses identified 7 regions meeting genome-wide significance for the anti saccade task, degraded stimulus Continuous Performance Test, abstraction/mental flexibility, spatial processing, and sensori-motor dexterity, with near significance for spatial memory. These regions contain genes of interest, including BASP1, NRG3, and HCN1. Many regions exceeding a genome-wide suggestive threshold of 10-5 were identified for all 11 endophenotypes.
Conclusions: These analyses have identified many genomic regions of interest that require further exploration and validation in the 1093 COGS-1 family members and 1034 COGS-2 cases and controls of African ancestry. It is important to note that we are investigating the genetic architecture of heritable neurocognitive and neurophysiological endophenotypes associated with schizophrenia risk. Understanding the molecular basis of these endophenotypes, many of which are recognized as treatment targets by the FDA, will pave the way for precision-based medicine.
Supported By: R01-MH065571, R01-MH065588, R01-MH065562, R01-MH065707, R01-MH065554, R01-MH065578, R01-MH065558
Keywords: Endophenotype, Genetics, GWAS, Neurocognition, Schizophrenia

S210. A Normative Chart for the Trajectory of Cognitive Functioning in a Genetically Selected Population: Longitudinal Findings From the International Brain and Behavior Consortium on 22q11.2 Deletion Syndrome

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Background: Individuals with 22q11.2 deletion syndrome (22q11DS), a genetic high-risk (25%) model of schizophrenia, show on average a modest decline in IQ between 8 and 24 years. This IQ pattern may represent a developmental phenotype that is specific to 22q11DS. To further characterize this, we constructed a 22q11DS-specific normative chart for cognitive development.
Methods: We used cross-sectional and longitudinal IQ data (Wechsler scales only) from 1871 individuals with 22q11DS (mean age 15.7, SD 7.4, years; n = 330 (17.6%) with schizophrenia), collected through the International Brain and Behavior Consortium (IBBC). After comprehensive quality control, we used a polynomial regression model, similar to what is used for standardized growth charts for height and weight, to construct normative charts for Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) for the age range 6 to 40 years.
Results: The 4th order polynomial regression provided a good fit, and allowed for the larger variability of IQ in very young age groups. On average, the 22q11DS population showed a gradual, modest decline in FSIQ, VIQ and PIQ. Consistent with our previous results, individuals who went on to develop schizophrenia showed a steeper decline, representing a negative deviation from their expected trajectory.
Conclusions: This study demonstrates both the feasibility and potential utility of a normative chart for cognitive development specific for a genetically selected high-risk population. The chart can be readily applied both in clinical care and research settings and may serve as an example for constructing similar normative charts in other high-risk groups and/or genetic disorders.
Supported By: NIMH
Keywords: Schizophrenia, Cognition, High-risk, Development, 22q11DS

S211. Towards Precision Medicine for Psychosis: Biomarkers for Hallucinations and Delusions

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Background: Schizophrenia and other psychotic disorders have as key pathognomonic symptoms hallucinations (perceptual abnormalities) and delusions (conceptual abnormalities). Psychiatric patients may have an increased vulnerability to psychosis, regardless of their primary diagnosis. As such, they may be a particularly suitable population in which to try to identify blood biomarkers for hallucinations and for delusions that are generalizable and trans-diagnostic.
Methods: First, we used a powerful longitudinal within-subject design in individuals with psychiatric disorders to discover blood gene expression changes between self-reported no hallucinations and high hallucinations states, and between no delusions and high delusions states. Second, we prioritized this list of candidate biomarkers with a Bayesian-like Convergent Functional Genomics approach, comprehensively integrating previous human and animal model evidence in the field. Third, we validated our top

biomarkers from discovery and prioritization in independent cohorts of psychiatric subjects with high scores on psychosis rating scales.
Results: We were able to show that the candidate biomarkers from the first three steps are able to predict hallucinations and delusions, and future hospitalizations with hallucinations and delusions, in independent cohorts of psychiatric subjects. We also used the biomarker gene expression signatures to interrogate the Connectivity Map database and identified drugs and natural compounds that can be repurposed.
Conclusions: Overall, given the negative impact of untreated psychosis on quality (and quantity) of life, the current lack of objective measures to determine appropriateness of treatment, and the mixed results with existing medications, the importance of approaches such as ours cannot be overstated.
Supported By: NIH, VA
Keywords: Gene Expression Profiling, Predictive Biomarkers, Psychosis, Blood

S212. Netrin Isoforms in Psychosis

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Background: To examine the association of Netrin isoforms with psychosis.
Methods: 300 subjects with schizophrenia and 300 controls were evaluated. Three SNPs (rs4132604-SNP1, rs2218404-SNP2 and rs1373336-SNP3 were genotyped in this study. All samples were run blind to diagnosis. (reverse). A case-control design was used for statistical comparison with the SPSS. Deviation from the Hardy-Weinberg equilibrium was examined using the Chi Square test and pairwise linkage disequilibrium.
Results: Strong pairwise linkage disequilibrium was found between the three SNPs rs4132604, rs2218404 and rs1373336 (all [D`] $>$ 0.60). Significant differences of haplotype containing rs4132604 alleles were found between cases and controls with GG ($p = .001$) and TG ($P = .0001$) between rs4132604 and rs2218404, GGT ($P=.0001$), TGT ($P = .01$) among the three SNPs. The allele frequencies of rs4132604 in psychotic cases was much different than among healthy controls ($p = .0001$).
Conclusions: Our study demonstrated positive association between rs4132604 and schizophrenia on the basis of the alleles (chi square = 7.912, $p = .005$) and genotype (chi square = 7.772, $p = .021$) frequency distribution differences between cases and controls. The occurrence of allele G was much higher than T alleles in rs4132604. This suggested that the chromosome that contained allele G (odds ratio = 1.423, 95% CI = 1.102-1.731) had a possible contribution to the susceptibility to schizophrenia. Our findings replicate Asian studies on Netrin variations in psychosis Our study was among the first to document this association in North American population and suggests that previous Asian work may be generalizable to other populations.
Keywords: Schizophrenia, Psychosis, Netrin

S213. Altered Patterns of Expression for Actin and Mitochondrial Markers Across the Working Memory Cortical Circuit in Schizophrenia

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Background: Working memory (WM) is mediated by a distributed cortical circuit that is functionally disrupted in schizophrenia. Dysfunction of the prefrontal cortical (PFC) node of this network is thought to reflect impaired actin regulation of dendritic spines on pyramidal neurons, leading to reduced pyramidal cell activity and a lower requirement for mitochondrial energy production. Here, we sought to determine if similar alterations are present in schizophrenia in other cortical regions of the visuospatial WM network
Methods: From 20 matched pairs of schizophrenia and unaffected comparison subjects, we quantified the expression of genes related to actin dynamics and mitochondrial function in total grey matter from PFC area 46, posterior parietal cortex area 7, and occipital cortex areas 17 and 18.
Results: In comparison subjects, the regional patterns of expression differed among actinregulating transcripts, whereas all mitochondrial markers increased in expression from anteriorto-posterior regions. In schizophrenia subjects, among the actin-regulating transcripts, CDC42 levels were lower in all regions, whereas the other transcripts did not show a consistent disease effect across regions. Levels of all mitochondrial transcripts (ATP5H, COX4I1, COX7B, and NDUFB3) assessed were lower in schizophrenia, although the magnitude of the disease effect differed across regions.
Conclusions: In schizophrenia, the expression of actin-regulating transcripts differ across cortical regions of the visuospatial WM network. In contrast, the disease effect on the expression of mitochondrial enzyme transcripts was conserved across regions, suggesting that lower energy production in multiple nodes of the WM cortical circuit may contribute to cognitive dysfunction in schizophrenia.
Supported By: MH103204
Keywords: Schizophrenia, Visuospatial Working Memory, Actin Polymerization, Mitochondral Enzymes, Cognitive Dysfunction

S214. Neuropil Contraction in Relation to Complement C4 Gene Copy Number in Independent Cohorts of Adolescent-Onset and Young Adult-Onset Schizophrenia Patients

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Background: A recent report suggested Complement 4 (C4A) gene copy number repeats (CNR) as risk factors for

schizophrenia. Rodent model suggested pathophysiological significance of these associations by demonstrating increased synaptic pruning. We, thus, predicted that C4A CNR would be positively correlated with increased neuropil contraction in the human brain among schizophrenia patients showing more prominent correlations in ventral regions among young adults and dorsal regions among adolescents since neuromaturation progresses dorsoventrally.
Methods: Whole-brain, multi-voxel, in vivo phosphorus magnetic resonance spectroscopy (31P MRS) assessed neuropil changes by estimating levels of membrane phospholipid (MPL) precursors and catabolites. Increased MPL catabolites and/or decreased MPL precursors indexed neuropil contraction. Digital droplet PCR-based assay was used to estimate C4A and C4B CNR. We evaluated two independent cohorts (young adult-onset early-course schizophrenia [YASZ=15] and adolescent-onset schizophrenia [AOSZ=12] patients), and controls matched for each group, n=22 and 15, respectively. Separate forward stepwise linear regression models were built for MPL catabolites and precursors for each group.
Results: YASZ cohort: Consistent with the rodent model data, C4A CNR positively correlated with neuropil contraction (increased pruning/decreased formation) in the inferior frontal cortex and inferior parietal lobule. C4B repeats correlated with neuropil contraction in the cerebellum and superior temporal gyrus. AOSZ cohort: C4A CNR positively correlated with neuropil contraction in the dorsolateral prefrontal cortex and thalamus while C4B repeats correlated with neuropil contraction in the prefrontal and subcortical regions.
Conclusions: C4A and C4B CNR are associated positively with indices of neuropil contraction in regions often implicated in schizophrenia that may not be neuromaturationally dependent.
Supported By: NIMH
Keywords: Complement Genes, Magnetic Resonance Spectroscopy, Synaptic Pruning, Schizophrenia, Neurodevelopment

S215. Aggregating Genetic and Brain Networks Associated With Risk for Schizophrenia via Spectral Clustering of Working Memory Activation and PGC2 Loci

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Background: Schizophrenia is often characterized by significant cognitive impairment, frequently probed using working memory tasks. Additionally, heritability is estimated to be near 80%, through many genetic factors of small effect. The PGC2-SCZ has established 108 significant schizophrenia-associated genetic loci. Here, we used spectral clustering of the relationship of each locus with working memory functioning to uncover schizophrenia-related genetic and brain networks underlying this risk.
Methods: 639 healthy adults completed N-back fMRI and genotyping. After imputation, FUMA-SNP2Gene identified lead SNPs for each of the 108 PGC2-SCZ loci and linear regressions of risk alleles with 2back-0back contrasts were performed, controlling for age, sex, performance and three genetic principal components. Spectral clustering separated whole-brain-SNP association images into k=2-15 clusters, revealing SNPs with similar brain activation patterns. Cluster validation measures determined the optimal solution. FUMA-Gene2Func identified gene ontology (GO) processes over-represented in each cluster (pBONF<0.05).
Results: Spectral clustering of each genetic locus's relationship with N-back activation identified an optimal 3-cluster solution: Cluster1) activation of DLPFC, SFG, IPL, fusiform and sensorimotor cortex, with over-represented GO processes of synaptic plasticity, CNS and striatal development, and neuronal migration; Cluster2) hippocampus, midcingulate and insula function with over-represented synaptic signaling/transmission, nicotine response, and cholinergic transmission; and Cluster3) diffuse white-matter associations that related only to glycoside metabolism.
Conclusions: This work aggregates both genetic and brain networks underlying schizophrenia risk. We identified three groups of loci showing distinct associations with working memory functioning, each associated with specific genetic pathways. These results may uncover subtypes of schizophrenia and highlight unique genetic mechanisms required for symptom manifestation.
Supported By: NIMH Intramural Program
Keywords: Spectral Clustering, Risk Loci, Working Memory fMRI, Schizophrenia, Gene Ontology

S216. MicroRNAs as Biomarkers for Treatment Response in Psychotic Disorders

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Background: Variants within microRNA (MIR) genes MIR219 (rs107822), MIR137 (rs1625579), and MIR206 (rs16882131) have been associated with disruption of glutamate signaling, poor cognitive performance, and altered expression of neurotrophic factors. We examined relationships between miRNA polymorphisms with clinical and neurocognitive outcomes in first-episode psychosis patients before and after antipsychotic treatment.
Methods: First-episode schizophrenia (n=110), bipolar disorder (n=15), and major depressive disorder with psychosis (n=10) patients were assessed before and after 6 weeks of antipsychotic therapy. IQ $\leq$70, age <15 years, substance/alcohol dependence and antipsychotic exposure $\geq$18 weeks were exclusion criteria. Baseline differences in symptoms, [Brief Psychiatric Rating Scale (n=135)], and cognition [neuropsychological battery composite z-score (n=131)], and changes in these parameters after treatment were analyzed using ANCOVA with covariates of age, sex,

ancestry estimates, and baseline scores in relation to genotypic data.
Results: MIR219 rs107822_CC subjects had lower baseline negative symptom scores compared to T carriers ($F(2,128)=3.652$, $p=0.029$). CC genotype has previously been identified as a protective genotype in schizophrenia. MIR206 rs16882131_TT subjects had higher positive symptom scores as compared to C carriers ($F(2,128)=3.368$, $p=.038$). Additionally, MIR206 rs16882131_C allele was associated with better negative symptom improvement after treatment ($F(1,97)=5.059$, $p=0.027$). Finally, the MIR137 rs1625579_T allele was associated with change in cognition after treatment ($F(1,92)=4.017$, $p=0.042$). Rs1625579_T allele, formerly linked as a risk allele with lower cognition and worse symptomatology, demonstrated greater improvement in cognition after treatment.
Conclusions: Associations of MIR206, MIR137, and MIR219 with cognition and symptom severity may serve as markers for antipsychotic treatment response and help identify mechanisms related to disease pathology.
Supported By: National Institute of Health (NIH) grant MH083888 to Jeffrey R. Bishop
Keywords: microRNA, Biomarkers, Treatment Response, Psychotic Disorders, First Episode Psychosis (FEP)

S217. The Dose Dependent Relationship Between Schizophrenia Polygenic Risk and Cognitive Variables in Schizophrenia Cases and Their Siblings

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Background: We evaluated the association of schizophrenia risk profile scores (RPS) with cognitive variables in 537 schizophrenia cases, 268 unaffected siblings, and 830 controls.
Methods: Participants provided demographic and clinical information, completed a cognitive battery, and provided blood for genetics analyses. Schizophrenia RPS were based on genetic variants identified by the Psychiatric Genetics Consortium. For better visualization of genetic dose/phenotype relationships, samples were divided into septiles based on schizophrenia RPS using a threshold of $pT<0.2$. We then used R graphing and ANCOVAs (SPSS) to depict and test for differences across the septiles in WAIS IQ and composite scores for general cognition ("g"), verbal and visual memory, processing speed, N-back, card sorting, and span, with attention to linear and non-linear contrasts, adjusting for age, sex and ancestry.
Results: In the schizophrenia sample, the effect of RPS septile was significant for "g" [$p=.013$], WAIS IQ [$p=.004$], and verbal memory [$p=.001$]. For siblings, septile significantly predicted "g" [$p=.004$], verbal memory [$p=.037$], and visual memory [$p=.031$]. Contrasts suggested a linear genetic dose relationship for most cognitive variables, such that higher levels of RPS were associated with lower variable scores (e.g., schizophrenia linear contrast for g: $p=0.001$). Non-linear contrasts (e.g., schizophrenia cubic contrast for g: $p=0.049$) may suggest somewhat muted and amplified cognitive effects, respectively, at the lowest and highest levels of RPS. No significant relationship with RPS was found for any cognitive variable in the control sample.
Conclusions: Schizophrenia RPS have an inverse, dose dependent association with cognitive variables in cases and unaffected siblings.
Supported By: NIH Division of Intramural Research Program
Keywords: Schizophrenia, Genetics, Polygenic Risk Score, Cognition, Verbal Memory

S218. A Potential Therapeutic Target of Plasma Free Fatty Acids in First-Episode Antipsychotic-Naïve Patients With Schizophrenia

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Background: Previous findings indicated that schizophrenia (SZ) patients have increased breakdown of membrane phospholipids. The present study is thus to test whether the resulting plasma FFAs are altered at early course of disease development, and if so, whether such changes can be affected by treatment of atypical antipsychotic drugs (AAPD).
Methods: Twenty-five first-episode antipsychotic-naïve patients (FEAN) with SZ were recruited to compare with 29 age and gender-matched healthy controls (HC). Blood samples were collected at baseline as well as 1-m, 6-m and 12-m after initial AAPD treatment. Plasma FFAs were quantitatively determined by capillary gas chromatography.
Results: (1) Decreased levels of plasma total FFAs in the FEAN-SZ were found significantly ($p < 0.002$) lower than those in HC subjects. (2) There was a robust increase of plasma FFAs in FEAN-SZ after 1-m AAPD treatment. However, after 12-m treatment, such differences were no longer present. (3) Significant correlations within several fatty acid families were shown in both groups, whereas other correlations were only found in the HC, but not in FEAN-SZ. Such insignificant correlations in baseline patients, however, may be normalized after 1-m AAPD treatment.
Conclusions: The present findings implies an imbalanced FFA biosynthesis in SZ, and such a decrease may reflect a depleted pool of FFAs during the early course of SZ development. Notably, the normalization of plasma FFA levels seen after 1-m treatment, waned with continued treatment over the next 11 months. This may reflect compensatory changes with longer-term treatment and reduced efficacy with respect to membrane phospholipid hydrolysis.
Supported By: Department of Veterans Affairs [Merit Reviews (JKY) and Senior Research Career Scientist Award (JKY)] and National Institute of Mental Health [MH58141 (JKY), MH64023 (MK)].
Keywords: Plasma Free Fatty Acids, Antipsychotic-Naïve, First Episode Schizophrenia, Atypical Antipsychotic Drug

S219. Modeling Subjective Relevance in Schizophrenia and its Relation to Aberrant Salience

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Background: In schizophrenia, increased aberrant salience to irrelevant events and reduced learning of relevant information may relate to an underlying deficit in relevance detection. So far, subjective estimates of relevance have not been probed in schizophrenia patients. The mechanisms underlying belief formation about relevance and their translation into decisions are unclear.
Methods: Using novel computational methods based on the Hiearchical Gaussian Filter, we investigated relevance detection during implicit learning in 42 schizophrenia patients and 42 healthy individuals. Participants underwent fMRI while detecting outcomes in a learning task. These were preceded by cues differing in color and shape, being either relevant or irrelevant. We defined relevance based on Bayesian precision and modeled reaction times as a function of relevance weighted unsigned prediction errors (UPE). For aberrant salience, responses to subjectively irrelevant cues were assessed.
Results: Participants learned the contingencies (Time effect:$F=2.6$,$p=.053$) and slowed down following unexpected events (Main effect of event type: $F=5.9$,$p=0.018$). Model selection revealed that individuals inferred the relevance of cue features and used it for behavioral adaption. Relevance weighted UPEs correlated with dorsal anterior cingulate cortex activation (([12 32 22], $t=4.2$, $p=0.032$) and hippocampus deactivation (([-32 -18 -14], $t=5.4$, $p=0.041$). In patients, the aberrant salience was increased ($t=2.7$, $p=0.036$) and correlated with decreased striatal UPE activation ([-14 4 -10], $t=5.21$, $p<0.001$) and negative symptoms ($\rho=0.334$, $p=0.031$).
Conclusions: This study demonstrates that relevance estimates based on Bayesian precision can reliably be inferred from observed behavior. This underscores the importance of relevance detection as an underlying mechanism for behavioral adaptation in complex environments and enhances the understanding of aberrant salience in schizophrenia.
Supported By: DFG SCHL1969/1-2, DFG SCHL 1969/2-2 as part of FOR 1617, SCHL 1969/4-1
Keywords: Schizophrenia, Bayesian Model, Reinforcement Learning, Computational Psychiatry, BOLD fMRI

S220. Neural Circuit Model of Pharmacological Interventions to Large-Scale Cortical Dynamics Applied to Clinical Neuroimaging

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Background: Computational models of large-scale human brain circuits provide a useful framework to study relationships between synaptic-level alterations associated with neuropsychiatric disorders and neuropharmacology, and systems-level observations from non-invasive neuroimaging such as fMRI. Previously, we developed a modeling framework that incorporates heterogeneity of local recurrent strengths across the cortical hierarchy captured by myelin map topography. We found that microcircuit heterogeneity substantially increased the fit of the model to empirical resting-state functional connectivity (rs-FC) in healthy subjects.
Methods: We proposed a biophysically-based large-scale computational model to investigate effects of pharmacological intervention on rs-FC. We fit the parameters of the model to capture rs-FC alterations in healthy subjects under acute subanesthetic administration of ketamine, an NMDA-receptor antagonist used as a pharmacological model of schizophrenia. Furthermore, we extended the model to simulate areal heterogeneity of receptor densities using maps derived from gene expression across the human brain.
Results: Ketamine-induced rs-FC alterations exhibits a hierarchical pattern of preferential effects in association vs. sensory cortex. We found that model simulation of global NMDA-receptor antagonism across cortex, which disrupts excitation-inhibition balance and interacts with the hierarchical gradient of recurrent strengths, captures this empirical pattern. The model also predicted hierarchical alterations in higher-frequency synaptic activity, consistent with observed ketamine effects from resting-stat MEG. Model fitting can be similarly applied to other pharmacological manipulations, or to neuropsychiatric disorders such as schizophrenia.
Conclusions: Our model provides a biophysically-based computational framework relating cortical heterogeneity to large-scale dynamics, enabling modeling of heterogeneous areal patterns of functional connectivity alterations under pharmacological manipulation and in neuropsychiatric disorders.
Supported By: R01MH112746, R01MH108590, TL1TR000141, Swartz Foundation, BlackThorn Therapeutics
Keywords: Computational Modeling, Ketamine, NMDA, Resting State fMRI, Schizophrenia

S221. Glutamate in Dorsolateral Prefrontal Cortex is Related to Working Memory Dependent Effective Connectivity in Patients Suffering From Schizophrenia: A Combined fMRI- and MRS-Study

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Background: Cognitive deficits are a core feature of schizophrenia. However, the underlying neurobiology is not fully understood. One candidate biochemical marker for the integrity of connectivity is glutamatergic neurotransmission. Here we tested for group differences in effective connectivity and for a possible association of connectivity with glutamate in dorsolateral prefrontal cortex (DLPFC) during working memory.
Methods: 42 patients and 41 healthy age and gender-matched controls performed a working memory task during an fMRI-session. We used dynamic causal modeling on a model space comprising regions of interest for a visual input, parietal (PC) and DLPFC. We calculated Bayesian model averages to obtain weighted connectivity parameters. Additionally, we used magnetic resonance spectroscopy (MRS) in order to estimate local glutamate concentration in DLPFC.
Results: Working memory dependent connectivity effects could be observed in the left hemisphere on backward connections (PC->DLPFC, HC: t=2.77, p=0.008; SZ: t=2.62, p=0.012). We found no group difference in parieto-frontal connectivity parameters and no difference in glutamate levels.

To explore possible effects of local Glutamate levels on connectivity, we correlated parameters for PC->DLPFC connectivity with glutamate levels. We found a negative association between parieto-frontal connectivity and glutamate in DLPFC in patients (rho=-0.47, p=0.0035,) but not in controls (rho=-0.12, p=0.53).
Conclusions: Although our data neither showed a group difference in connectivity nor in glutamate levels, our findings suggest that glutamate is differentially related to working memory dependent connectivity from parietal to frontal areas in patients as compared to controls. This might indicate a possible marker for an allostatic compensation of NMDA-receptor dysfunction in schizophrenia patients.
Supported By: DFG SCHL1969/1-2 SCHL1969/2-2
Keywords: Schizophrenia, Functional Brain Connectivity, Glutamate, DLPFC, Dynamical Causal Modeling

S222. Decreased Striatal Reward Prediction Error Coding in Unmedicated Schizophrenia Patients

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Background: Reinforcement learning involves flexible adaptation towards a changing environment and is driven by dopaminergic reward prediction error (RPE) signaling in the midbrain and projecting regions, such as the striatum. Schizophrenia patients (Sz) show heightened dopamine levels in the striatum and deficits in reinforcement learning which may be mediated by disrupted RPE signaling. Using model-based fMRI, this study aims to assess these signals during reversal learning in unmedicated Sz and healthy individuals.
Methods: 19 Sz and 23 healthy controls completed a reversal learning paradigm during fMRI. A Rescorla Wagner learning model was fitted against the individual choice data using a softmax function. Individual RPE trajectories from the fitted model were correlated with the BOLD response during feedback onset. Parameter estimates of ventral striatal RPE trajectories were correlated with psychopathology scores.
Results: Sz chose the correct stimulus less often compared to healthy individuals. Across all participants, the RPE trajectories correlated with BOLD response in the bilateral ventral striatum ([-10 12 10], t=7.40, pFWE<0.001; [10 12 -10], t=6.56, pFWE=0.006). Sz displayed decreased RPE coding in the right ventral striatum compared to healthy individuals ([14 14 -10], t=3.69, pSVC for nucleus accumbens=.015). In patients, parameter estimates from the right ventral striatum correlated negatively with the PANSS total score (Spearman's rho =-0.55, p=0.018).
Conclusions: While RPE coding seems to be intact in patients receiving antipsychotic medication, our findings are in line with previous studies in unmedicated Sz. Therefore, deficient RPE coding may reflect a characteristic of the disorder of schizophrenia and does not result from antipsychotic medication.
Supported By: DFG SCHL1969/1-2, DFG SCHL 1969/2-2 as part of FOR 1617, SCHL 1969/4-1
Keywords: Schizophrenia, Reinforcement Learning, BOLD fMRI, Prediction Errors

S223. Heterogeneity in Cortical Microstructure is Associated With Cognition

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Background: Cognitive impairment is frequently reported in individuals at risk for developing schizophrenia, and is thought to be associated with abnormalities in gray and white matter. Whereas deficits in the structural properties of white matter have been observed, studies have yet to explore the microstructure of cortical gray matter. Diffusion MRI can be used to characterize the microstructure of gray matter, creating an unprecedented opportunity to explore the association between gray matter microstructure and cognitive abilities. The present study is the first one to use diffusion MRI to investigate alterations in cortical gray matter microstructure in individuals with 22q11.2 Deletion Syndrome (22q11DS), a genetic disorder with an increased incidence of psychosis and cognitive deficits.
Methods: This study employs a novel diffusion MRI measure, the Heterogeneity of Fractional Anisotropy (FA), to examine variability in the microstructural organization of the cortex in healthy young adults (N=30) and those with 22q11DS (N=56).
Results: Compared to controls, individuals with 22q11DS revealed increased Heterogeneity of FA in cortical association (p=0.003, d=0.86) and paralimbic (p<0.0001, d=1.2) regions, whereas no significant differences were found between groups in primary cortical regions. Heterogeneity of FA in association (r=-0.334, p=0.002) and paralimbic (r=-0.398, p=0.0001)

regions correlated negatively with Full Scale IQ across all participants.
Conclusions: These findings suggest that increased variability in microstructural cortical organization may be a neural correlate of cognitive impairment in healthy and psychiatric populations. Additionally, they suggest that abnormalities in the structural composition of specific gray matter regions may contribute to a vulnerability for the development of schizophrenia.
Supported By: RO1MH064824, R21MH106793, R01MH097979, AG042512, AT008865, R01AG042512, R21AT008865, R21DA042271, R01MH111917, R01HD09064, VA Merit Award I01 CX000176-06
Keywords: 22q11 Deletion Syndrome, Gray Matter Microstructure, Cognitive Impairment, Diffusion Tensor Imaging (DTI)

S224. Dynamic Functional Network Connectivity in Schizophrenia and Autism Spectrum Disorder

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Background: Autism spectrum disorder (ASD) and schizophrenia (SZ) co-occur at elevated rates, and share similar social deficits and genetic risk factors. However, few studies have directly compared these disorders. Dynamic functional network connectivity (dFNC) is a recent analysis method that explores temporal patterns of brain connectivity. We examined dFNC in SZ, ASD and healthy controls (HC).
Methods: Resting-state fMRI was collected from 100 individuals: 33 SZ, 33 ASD, 34 HC. High-order independent component analysis (ICA) was performed, followed by dFNC analysis (window=30s, step=1TR, k-means clustering) using the GIFT toolbox. Number of transitions (NT), number of states (NS), fraction time (FT), and dwell time (DT) were calculated per subject. These measures were compared between groups using ANOVA and post-hocs, and correlated with symptoms.
Results: Three re-occurring functional connectivity states were identified: 1) cortico-cortical, 2) intra-network, and 3) cortico-cortical with strong visual-sensory-motor connectivity. Compared to HC, both clinical groups showed decreased NS [ANOVA,$P=0.001$] and increased state-2 FT (SZ were also reduced compared to ASD [ANOVA,$P<0.001$]), and decreased in state-1 FT [ANOVA,$P<0.001$]. SZ also showed decreased NT [ANOVA,$P<0.001$] and state-3 FT [ANOVA,$P<0.001$], and increased state-2 DT [ANOVA,$P<0.001$] compared to HC and ASD, and decreased state-1 DT [ANOVA,$P=0.001$] compared to HC. NT correlated negatively with the positive and negative syndrome scale (PANSS) total score [Spearman,$P=0.028$; $r=-0.282$].
Conclusions: Both SZ and ASD demonstrated a pattern of restriction (SZ>ASD), specifically being "stuck" in state of weak intra-network connectivity. Differences and commonalities between ASD and SZ were state-specific, and the overall number of transitions between dFNC states correlated with clinical severity.
Supported By: RO1
Keywords: Schizophrenia, Autism Spectrum Disorder, Resting State Functional Connectivity, Dynamic Functional Network Connectivity (dFNC), Dynamic FNC

S225. Transdiagnostic Multimodal Neural Correlates of Cognitive Control in Psychosis: Dimensions of Alteration From Healthy to Disease

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Background: Psychosis is present in schizophrenia and other disorders. Persons with psychosis exhibit alterations in cognitive control, related to alterations in structural, resting-state, and task functional imaging data. However, many studies are unimodal, and links across modalities are unclear. Thus, we applied multimodal analyses examining transdiagnostic patterns of neural variation related to cognitive control in psychosis.
Methods: Structural, resting, and 2-back task imaging and behavioral data were analyzed for 31 controls, 27 persons with psychotic bipolar, and 23 persons with schizophrenia spectrum disorders. Data were collected and processed identically to the Human Connectome Project (HCP), enabling assessment of relationships with prior multimodal cognitive control analyses. Two independent components (ICs) predictive of cognitive control in the HCP derived using multiset canonical correlation analysis + joint independent component analysis (mCCA+jICA) were applied to present data. Subject-specific weights on these ICs were correlated with cognitive control performance. Next, mCCA+jICA was applied de-novo and resultant IC subject-specific weights correlated with cognitive control.
Results: Partial correlations using a-priori ICs identified a partially significant relationship to cognitive control in psychosis (2-back fMRI: $r=0.366$ $p=0.001$, $r=0.300$ $p=0.008$; others n.s.). De-novo mCCA+jICA identified a single group-discriminative IC, which was also significantly related to cognitive control (structural: $r=0.263$, $p=0.020$; resting-state: $r=0.221$, $p=0.051$; 2-back $r=0.293$, $p=0.009$). Contributing structural regions included insular, somatomotor, cingulate, and visual areas; task regions included precentral, posterior parietal, cingulate, and visual areas.
Conclusions: Analyses partially replicated a-priori normative results in psychosis data and suggests joint contributions of

identified regions relating to cognitive control across healthy-to-psychosis spectrum.
Supported By: 5F30MH109294; 5R01MH104414;
Keywords: Multimodal Neuroimaging, Psychosis, Transdiagnostic, Cognitive Control

S226. Ranking Resting-State Functional Connectivity Deficits in Schizophrenia Using ENIGMA rsfMRI and DTI Approaches

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Background: Altered brain connectivity is implicated in the development and clinical burden of schizophrenia. We measured and compared effect sizes (ES) for these phenotypes using Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) rsfMRI and DTI analysis pipeline in three MPRC cohorts with diverse acquisition parameters/protocols. Here, we focused the functional connectivity (FC) between the nodes of common resting state networks (RSNs) and microstructure of white matter tracts using fractional anisotropy (FA) to get more insight into the neural correlates of connectivity deficits in schizophrenia.
Methods: Three cohorts of schizophrenia patients (n=261, 161M/100F; age=11-63 years) and controls (n=327, 146M/211F; age=10-79 years) were ascertained with three 3T Siemens MRI scanners. We used the single-modality ENIGMA rsfMRI and DTI preprocessing pipeline to extract FC for eight major RSNs using seed-based and dual-regression approaches and FA values for twenty white matter tracts. We tested for case control differences in all cohorts together as well as each cohort independently. We aggregated statistics from the three cohorts and further tested whether ESs were consistent across cohorts.
Results: Patients had significantly ($p<0.01$; multiple correction, ES: 0.2-0.6) lower resting state functional connectivity than controls across cohorts. Patients also showed significantly ($p<0.01$; multiple correction, ES: 0.2-0.8) reduced FA values for whole-brain and tract-wide measurements. The ESs were similar between FC and FA metrics and varied between 0.2-1.0 for each cohort.
Conclusions: This is the first study to show consistency in functional and structural connectivity metrics across diverse cohorts in schizophrenia and demonstrated the impact of lower FC and FA on cognitive and behavioral measurements.
Supported By: U54EB020403;R01MH112180
Keywords: Effect Size, Functional Connectivity, Schizophrenia

S227. Decreased Peak Alpha Frequency and Impaired Visual Evoked Potentials in First Episode Psychosis

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Background: Abnormal spontaneous and evoked oscillations have been reported in several studies of patients with psychotic disorders. Peak alpha frequency has been proposed as marker of illness chronicity (Harris et al., 2006). In the present study, we used high-density EEG (hd-EEG) to measure peak alpha frequency in patients with first episode psychosis (FEP) and to compare peak alpha frequency to brain resonances in multiple frequencies using steady- visual evoked potentials (SSVEPs).
Methods: Hd-EEG (128 channels) was recorded from 22 FEP patients and 22 healthy controls during eyes-closed resting state and eyes-closed photic stimulation at 1 Hz, 4 Hz, 10 Hz, 20 Hz, and 40 Hz. Alpha power, peak alpha frequency, and SSVEP amplitude were analyzed using ANOVA and statistical non-parametric mapping.
Results: FEP patients had significantly lower peak alpha frequencies (9.75 Hz vs 10.41 Hz, $p=.02$, Cohen's $d = 0.73$). There was no significant difference in alpha power. FEP patients showed significantly smaller increases in EEG power in the stimulation band in response during SSVEP ($F(1,184) = 5.3$, $p = .02$). For both controls and FEP patients, stimulation at 1 Hz was statistically significantly less able to produce increases in the stimulation frequency band ($F(4,184)=7.1$, $p < .00001$). There was no correlation between peak alpha frequency and VSSEP power increases ($r = .25$, $p = .10$).
Conclusions: Even in early stages of illness, psychotic disorders are associated with decreased alpha peak frequency and broadly impaired evoked resonances. This suggests that FEP is related to multiple patterns of dysconnectivity in cortico-cortico and cortico-thalamic networks.
Supported By: Stanley Center at the Broad Institute of Harvard and MIT
Keywords: First-Episode Psychosis (FEP), Electroencephalography (EEG), Visual Evoked Potential, Resting State

S228. Measuring the Relationship Between Specific Phosphorylation of DISC1 and Cortical Thickness in Psychotic Disorders

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Background: Our previous work showed that phosphorylation of DISC1 at serine-710 was a key switch for neural fate in developing mouse brains. We have recently found a reduction in serine-713 (corresponding to mouse serine-710) phosphorylation of DISC1 (pS713-DISC1) in biopsied tissue of patients with psychotic disorders. Here we investigate the relationship between pS713-DISC1 and cortical differences in 3 structures thought to be involved in psychotic disorders: anterior cingulate cortex (ACC) and dorsal lateral prefrontal cortex (DLPFC) and planum temporale (PT). We found a significant relationship between pS713-DISC1 and ACC thickness.
Methods: 3T MRI scans, clinical and neuropsychological data were obtained. FreeSurfer's atlas-based registration was used to label regions of interest. Labeled cortical depth maps (LCDM) were calculated from each grey matter (GM) voxel to

the GM-WM boundary. We tested whether PDISC1 was an important predictor of 90% LCDM when fit to a log-linear fixed effects model covarying for age. Brief test of attention (BTA) scores were fit to a linear fixed effects model covarying for education.
Results: The MRI analysis was conducted on 16 healthy controls (HC) and 20 patients with psychotic disorders (PD); BTA analysis was conducted on 27 HC and 27 PD. There was a significant (p=.025) relationship between pS713-DISC1 and 90% LCDM of the left ACC. There was also a significant (p=.0374) relationship between pS713-DISC1 DISC1 and BTA score.
Conclusions: The results indicate that pS713-DISC1 levels correlate with ACC thickness, a region thought to regulate attention. pS713-DISC1 also correlates with BTA suggesting that pS713-DISC1 relates to ACC both structurally and functionally.
Supported By: P41EB015909
R01MH105660
Keywords: Neuroanatomy, Structural MRI, DISC1, Psychotic Disorders, Cortical Thickness

S229. A Voxel-Wise Multimodal Mapping of Structural and Functional Thalamic Dysconnectivity in Schizophrenia

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Background: Structural and functional brain connectivity alterations play a key role in the pathophysiology of psychiatric illness. Specifically, recent evidence implicates thalamic dysconnectivity as a potential neural marker of schizophrenia (SCZ). Despite the abundance of diffusion weighted imaging (DWI) and resting-state functional MRI (rsfMRI) studies in this population, few have investigated simultaneous structure-function connectivity abnormalities in thalamic circuits.
Methods: Multimodal thalamic dysconnectivity was assessed in SCZ patients (N=46) and a demographically matched healthy control group (N=53). DWI-derived probabilistic tractography and functional connectivity approaches were used across two thalamic nuclei. Neuroimaging data were collected and processed according to the next-generation acquisition and analysis methods developed by the Human Connectome Project. Type I error correction was performed using PALM non-parametric permutation-based methods.
Results: Results indicate robust and reliable solutions for both BOLD-derived functional connectivity and DWI-derived structural connectivity measures across prefrontal-projecting and sensorymotor-projecting thalamic nuclei. DWI-derived structural connectivity measures reveal a distinct and complex pattern of changes that do not cleanly follow functional alterations. Multivariate multimodal effects computed via PALM indicate that structure-function combinations generate novel and unique insight into thalamocortical disruptions in SCZ.
Conclusions: This study is among the first to demonstrate the feasibility of combining DWI and rsfMRI modalities on a voxel-wise basis to test multimodal structure-function thalamocortical alterations in SCZ. Results suggest that structural and functional connectivity patterns can be combined to jointly yield markers of disease severity, which can be iteratively refined to serve as a multivariate marker of psychiatric illness.
Supported By: NIH Early Independence
Keywords: Resting State Functional Connectivity, Structural Connectivity, Thalamus, Multimodal Neuroimaging, Schizophrenia

S230. Convergence of Specifically Altered Intrinsic Brain Connectivity and Aberrant Brain Volume in Schizophrenia Transdiagnostic Multimodal Meta-Analysis of Resting-State Functional and Structural MRI

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Background: Brain changes in schizophrenia have been shown by numerous imaging studies and corresponding meta-analyses, particularly concerning intrinsic functional connectivity (iFC) of ongoing brain activity, measured by resting-state functional MRI, and gray matter volume (GMV) of distributed brain regions, measured by structural MRI. However, it is unknown (i) which iFC-changes are specific to schizophrenia compared to those of other psychiatric disorders, and (ii) whether such specific iFC-impairments converge with GMV-changes. To address this question of specific and substantial dysorganization of intrinsic connectivity in schizophrenia, we performed a transdiagnostic and multimodal meta-analysis of resting-state functional and structural MRI studies in schizophrenia and other psychiatric disorders.
Methods: Multiple databases were searched until June 2017 for whole-brain seed-based iFC-studies in schizophrenia, addiction, anxiety, bipolar, and major depressive disorders, and for voxel-based morphometry studies in schizophrenia. Coordinate-based meta-analyses were performed to detect schizophrenia-specific hyper-/hypoconnectivity of intrinsic brain networks (compared to each of the other disorders separately, as well as conjunct across all comparisons) and its overlap with GMV-changes in schizophrenia (multimodal conjunction analysis).
Results: For iFC-meta-analysis, 173 publications with 4962 patients and 4575 controls and for GMV-meta-analysis, 127 publications comprising 6311 patients and 6745 controls were included. Schizophrenia-specific iFC-dysconnectivity, which was consistent across contrasts versus distinct disorders, was found in limbic, fronto-parietal-executive, default-mode, and

salience networks. Reduced GMV and schizophrenia-specific dysconnectivity converged on insula, striatum, and thalamus.
Conclusions: Results demonstrate specific and substantial dysorganization of intrinsic connectivity in schizophrenia in insula, striatum, and thalamus.
Supported By: Studienstiftung des deutschen Volkes; Bundesministerium für Bildung und Forschung; Deutsche Forschungsgemeinschaft; Kommission fuer Klinische Forschung of the Klinikum rechts der Isar der Technischen Universitaet Muenchen
Keywords: Schizophrenia, Functional MRI, Functional Connectivity, Disorder-specificity, Gray Matter Volume

S231. Intracortical and Superficial White Matter Microstructural Changes After a First Episode of Psychosis

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Background: Multiple scales of evidence point towards white matter abnormalities in and around the cortical mantle in psychosis. Here we use quantitative MRI to better pinpoint such changes, using a direct measure of T1 relaxation time both intracortically and within superficial white matter in first episode of psychosis(FEP) patients.
Methods: Structural MRI was acquired for 18 patients and 21 controls (15 and 19 longitudinally, respectively). Surfaces at 35%-65% equidistant cortical depths (i.e. intracortical qT1), and 1mm below the grey-white matter boundary (i.e. Superficial White Matter [SWM]) were extracted from T1-weighted scans. Quantitative T1 (qT1) values were sampled along each surface at 81,924 points on MP2RAGE scans. Linear models were used to assess baseline group differences in qT1, calculate qT1 rate of change(Δ), and examine associations between positive symptoms at baseline and ΔqT1.
Results: Cross-sectionally, patients had increased SWM qT1, i.e. longer relaxation times, in left somatomotor regions and right cingulate. Longitudinally, decreases in intracortical and SWM qT1 were observed in patients in frontal regions. Positive symptoms at baseline positively correlated with ΔqT1 within intracortical layers of left fusiform and prefrontal cortex. All results RFT-corrected($p<0.05$).
Conclusions: This study links dynamic changes in quantitative MRI to baseline clinical profiles. Given that white matter is characterized by shorter T1 relaxation times, increases in qT1 at baseline in patients points towards possible demyelination within SWM. Longitudinal data suggest a FEP may trigger reorganisation of SWM and intracortical white matter, and the degree to which the brain engages in this reorganisation process may be driven by severity of positive symptoms at baseline.
Supported By: Canadian Institutes of Health Research (CIHR)
Keywords: Quantitative Imaging, First Episode Psychosis, White Matter Microstructure, Positive Symptoms

S232. Effects of Incentive Presentation on Spatial Working Memory Performance

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Background: The strength of reward representation is a key influence on motivated, goal-directed behaviors. Little is known about how incentives influence neural cognitive control circuits. We examined the effects of trial-by-trial and contextual incentive presentation on spatial working memory (WM) performance using functional magnetic resonance imaging (fMRI).
Methods: 33 healthy adults performed a spatial WM task under the influence of monetary incentives. The possibility for monetary reward or loss was presented in a trial-by-trial manner and in a contextual manner. Images were collected using multi-band sequences and parameters consistent with protocols from the Human Connectome Project (HCP). Preprocessing protocols were consistent with the HCP pipeline. Permuted statistics were used to examine fMRI results.
Results: WM accuracy improved when the possibility for monetary reward or loss was presented in a trial-by-trial manner ($p<0.001$, both), and in a contextual manner ($p<0.01$, both). The neutral spatial WM task engaged expected frontal, parietal, motor and visual cortices ($p<0.05$). Examination of this map conjuncted with a thresholded map of trial-by-trial incentive conditions demonstrated increased percent signal change in visual, motor and anterior cingulate cortices during incentive conditions; in contrast, prefrontal and parietal cortices demonstrated relatively decreased signal change. The conjuncted contextual map showed an overall similar, but attenuated, pattern.
Conclusions: Spatial WM performance improved when rewarding and loss-avoiding incentives were presented in a trial-by-trial and contextual manner. Distinct patterns of neural activation appeared to encode the influence of trial-by-trial and contextually presented incentives on spatial WM. Future work may involve connectivity analyses, and translation to psychiatric patient populations.
Supported By: Thomas P. Detre Fellowship
Keywords: Working Memory, Reward Processing, Brain Imaging, fMRI, fMRI, Schizophrenia

S233. Sex-Specific Overlapping Structural and Functional Circuit Differences in Youth With Psychosis Spectrum Symptoms

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Background: Functional connectivity differences in the cortico-striatal-thalamic-cortical (CSTC) circuit, as well as altered subcortical region volumes have been observed in schizophrenia. In this study, magnetic resonance imaging was used in a large child and youth sample aged 11-21 years (n=1134) to examine this circuit in children with psychosis spectrum (PS) symptoms (n=312).
Methods: Structural subregions of the thalamus and striatum were identified using the segmentation tool MAGeT Brain. Functional subregions were segmented based on resting-state functional connectivity with brain networks. Average BOLD signal time series from functional subregions were correlated vertex-wide with cortical surfaces. FSL's PALM was used to examine main effects and interactions between PS groups and sex on functional connectivity with TFCE. Age, in scanner motion, and WRAT score were included as covariates and results were corrected using FWER.
Results: There was a consistent pattern of significantly increased volumes in girls with PS symptoms, but decreased volumes in boys with PS symptoms compared to non-PS youth in the bilateral posterior putamen of the striatum ($F=9.26$, $pFDR=0.006$) and multiple thalamic nuclei ($F=9.85$, $pFDR=0.004$). Overlapping with striatal structural findings, decreased functional connectivity was found in PS youth between the right posterior putamen (corresponding to the dorsal attention network) and occipital areas ($pFWE=0.005$). This pattern was found to be driven by differences specifically in PS boys and not PS girls ($pFWE=0.004$).
Conclusions: Our findings indicate sex-specific differences in the CSTC circuit in youth and may provide insight into diverging neural mechanisms underlying the development of psychosis and differences in clinical features between males and females.
Keywords: Sex Differences, Psychosis, Cortico-Striatal-Thalamic-Cortical Circuit, Resting-State fMRI, Structural MRI

S234. Psychosis Risk is Associated With Decreased Resting-State Corticostriatal Connectivity With the Default Mode Network but Intact Connectivity With the Frontoparietal Network

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Background: Psychosis is associated with aberrant salience and increased dopamine in the anterior dorsal striatum. Critically, the anterior dorsal striatum is connected to the default mode network (DMN) and, to a lesser extent, the frontoparietal network (FPN). The DMN is involved in self-relevance processing, suggesting that psychosis might be associated with abnormal connectivity between the striatum and the DMN. However, no previous study has directly examined striatal to DMN or FPN connectivity in psychosis risk.
Methods: In Study 1, we examined resting-state connectivity between (a) striatal DMN and FPN subregions with (b) cortical DMN and FPN in psychosis risk (n=18) and controls (n=19). In Study 2, to determine if decreased striatal to DMN connectivity was specific to psychosis risk or current distress, we examined the relationship between connectivity and distress in individuals with an emotional distress disorder (N=25).
Results: In Study 1, there was a Network x Group interaction, $F(1,35)=7.33$, $p<.01$, $\eta p2=.17$. Compared to controls, psychosis risk exhibited decreased connectivity between the striatum and cortical DMN, $F(1,35)=4.30$, $p<.05$, $\eta p2=.11$, and intact (if anything, increased) connectivity between the striatum and cortical FPN, $p=.326$, $\eta p2=.03$. Additionally, current distress in psychosis risk was associated with decreased connectivity between the striatum and cortical DMN, $rs<-.33$, $ps<.05$. In contrast, in Study 2 current distress in emotional disorders was associated with evidence of increased striatal to cortical DMN connectivity, $rs<.35$, $ps>.084$.
Conclusions: Results suggest that decreased striatal to DMN connectivity might be involved in psychosis risk and aberrant salience. Future research could examine if decreased connectivity predicts conversion to psychosis.
Supported By: NIMH T32 MH014677; NIMH MH100359; University of Missouri Research Funds
Keywords: Striatum, Psychosis Risk, rs-fMRI, DMN, FPN

S235. Artifact Identification and Removal in Simultaneous Multi-Slice (Multiband) fMRI

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Background: Simultaneous multi-slice (multiband) fMRI is a newly-available acceleration technique that dramatically increases spatiotemporal resolution but presents unique methodological challenges that must be addressed to produce reliable and reproducible findings in psychiatric neuroimaging.

We demonstrate the presence of a previously-undescribed signal artifact in multiband fMRI data that produces substantially elevated correlations between timeseries in slices acquired simultaneously, and propose a correction method. Additionally, we demonstrate that existing approaches to minimizing motion-induced artifacts in resting state functional connectivity (RSFC) using volume censoring are largely ineffective in multiband data and present an effective alternative.
Methods: Multiband slice artifacts were identified in both phantom and in vivo RSFC data (N=10) on both Siemens and GE scanners by obtaining the correlations between average voxel time series within each slice. Regression-based estimation of the shared signal across simultaneously-acquired slices was used to partially correct this artifact.

Standard volume censoring approaches were compared (N=500) to a novel approach that employs low-pass filtering (LPF) of motion parameters prior to estimation of framewise motion to eliminate the impact of respiration-related motion.
Results: Mean slice time series showed elevated correlations between simultaneously acquired slices compared to adjacent slices (mean difference in Pearson $r=0.3677$, $p<0.0001$). Regression-based correction largely attenuated this elevation ($mean=-0.2494$, $p<0.0001$).

LPF-based volume censoring produced substantially larger changes in RSFC correlations across ROIs than standard volume censoring, while removing fewer frames (all $p<0.0001$).
Conclusions: These two novel preprocessing methods successfully address significant sources of signal artifact in multiband RSFC data, and may represent critical methodological advances for psychiatric neuroimaging.
Supported By: NIH Grant K01MH107763 (Dr. Van Snellenberg); NIH Grant 5T32GM008444 (Stony Brook Medical Scientist Training Program)
Keywords: Resting-State fMRI, Artifact Rejection, Methods, Simultaneous Multi-Slice (multiband) fMRI, Biostatistics

S236. Neuromelanin-Sensitive MRI: A Novel, Non-Invasive Proxy Measure of Dopamine Function in Neuropsychiatric Illness

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Background: Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) has proven to be a sensitive neuroimaging marker for degeneration of dopamine neurons in Parkinson's disease but its utility as a marker of dopamine function in non-neurodegenerative conditions remains unclear.
Methods: We validated NM-MRI in the substantia nigra (SN) ex vivo, against spectrophotometric measurements of regional NM concentration in post-mortem tissue ($n=7$ specimens of the midbrain). We also validated this technique in vivo, against a Positron Emission Tomography (PET)-based measure of dopamine release capacity (based on amphetamine-induced displacement of the radiotracer [11C]raclopride) obtained in individuals without a neurodegenerative condition ($n=18$). To test its utility as a proxy for psychosis-related dopamine dysfunction, we collected data in 33 unmedicated individuals with schizophrenia, 25 individuals at high risk for psychosis, and 50 healthy controls. For voxelwise analyses, we used a permutation-based method for correction for multiple comparisons.
Results: Regional NM-MRI signal intensity in post-mortem midbrain specimens highly correlated with regional neuromelanin concentration ($t(114)=2.73$, $p=0.007$, mixed-effects model). Voxelwise analysis within the SN in vivo revealed a cluster where NM-MRI signal-to-noise positively correlated with striatal dopamine release capacity ($rho=0.55$, $p<0.05$). Voxelwise analyses in the psychiatric populations identified overlapping clusters where higher NM-MRI signal-to-noise in the SN correlated with more severe psychotic symptoms both in patients with schizophrenia and in individuals at clinical high risk (conjunction $p<0.0001$).
Conclusions: Our results indicate that NM-MRI signal reflects dopamine system function and captures a psychosis-related phenotype. Future work should evaluate the utility of NM-MRI as a predictive biomarker for treatment response or illness conversion in at-risk populations.
Supported By: Dana Foundation, NIMH, Fonds de Recherche du Quebec, Sante
Keywords: Psychosis, Neuromelanin-Sensitive MRI, Dopamine, Schizophrenia, PET Imaging

S237. Transcranial Direct-Current Stimulation (tDCS) in Patients With Ultra-Treatment-Refractory Auditory Hallucinations

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Background: tDCS, a noninvasive neurostimulation treatment, has shown improvements in treatment-resistant auditory hallucinations (AH) in outpatients with schizophrenia. Our aim was to test tDCS for auditory hallucinations in ultra-treatment resistant schizophrenia inpatients.
Methods: 28 inpatients with DSM-V schizophrenia and long-standing treatment resistance and persistent auditory AH participated in assessments with blinded raters at baseline, endpoint and 4-week follow-up [PANSS, Auditory Hallucinations Rating Scale (AHRS) and MCCB cognitive battery]. Participants were randomized to active vs. sham tDCS treatment. The Chattanooga, dual channel CHA-1335 stimulator was used for the delivery of 2 mA current.
Results: 28 subjects were enrolled (tDCS, $n = 13$; Control, $n = 15$). 3 subjects dropped out of the active tDCS and 5 subjects of the control treatment (early discharge). Repeated Measures ANOVA showed a significant difference for the AH total score, frequency and number of voices over time ($p < 0.05$), with greater reduction for the tDCS group. Improvements were maintained after 4 weeks. No significant change was observed for PANSS positive symptoms or total score, nor for the PANSS Hallucinatory Behavior item. Working Memory improvement was significant ($p = 0.048$) for the tDCS group.
Conclusions: Subjects who received tDCS treatment showed a significant reduction in the frequency, number of voices, and total scores of their auditory hallucination with persistent improvement, indicating that patients who have been ultra-resistant to antipsychotic treatments can respond to tDCS.
Keywords: Treatment Resistant Schizophrenia, Auditory Hallucinations, Neurostimulation

S238. Positive Memory Recollection in People With and Without Schizophrenia: A Narrative Approach

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Background: Narrative approaches can help uncover meaningful differences in people with and without schizophrenia (SZ) in terms of how they construct and derive meaning from their own emotional life events and memories of those events.

In this narrative study, we sought to better understand the ways in which people with and without SZ describe emotions in positive memory recollections.
Methods: We recorded and transcribed interviews with 25 people with SZ and 24 controls (HC) that asked participants to recall and describe a positive memory, and experience the positive emotion from that particular memory. We coded for content, vocal expression, clarity, and laughter, and counted the emotions described during the recollection. We also asked participants to report on their experienced emotion following the memory recollection. We hypothesized that people with SZ would use more negative emotion words, fewer positive words, be less vocally expressive, and include others less often as compared to HC.
Results: We found that people with SZ described their memories less clearly ($p=0.03$), laughed less ($p<0.001$), were less vocally expressive ($p<0.001$), described experiences with fewer people ($p=0.02$), but did not differ in positive and negative emotion word usage ($p>0.05$).
Conclusions: Our results suggest that certain areas of emotional organization and expression (e.g., clarity and vocal expression) are not necessarily related to how emotion words are conveyed in narratives, suggesting it is important to distinguish and separate these ways of conceptualizing emotion.
Keywords: Schizophrenia, Emotion, Narrative

S239. Sub Domains of Negative Symptoms in Individuals at Clinical High Risk for Psychosis

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Background: Current risk criteria for the Clinical High Risk (CHR) state include only positive symptoms, despite the recognition of negative symptoms as clinically important characteristics of the prodrome. In order to explore the role and associations of negative symptoms in CHR, we need to understand whether they are a unified construct, or whether, as had been found in psychotic disorders, there may be two distinct factors, with distinct clinical associations.
Methods: Principle Axis Factoring was conducted using the severity scores of the six negative items of the Structured Interview for Psychosis-Risk Syndromes (SIPS) in 214 individuals meeting the SIPS criteria for CHR. The Global Functioning: Social and Role (GFS and GFR) scales were used to assess functioning and the Calgary Depression Scale (CDS) to assess mood. Pearson's Product-Moment Correlation and linear regression were used to test the relationship between factors and clinical presentation.
Results: Factor analysis revealed two factors: Negative Emotion and Negative Volition. Both factors were highly correlated with poor social and role function, and depression. Linear Regression showed both factors predicted poor social function, but poor role function and depression were predicted by only the volition factor.
Conclusions: This finding distinguishes between the decrease in the experience and expression of emotion and decreased volition in CHR individuals, which reflects the pattern found in psychotic disorders. These factors have different clinical associations and therefore should be considered independently. Furthermore, the Ideational Richness item did not load on either factor, suggesting this item is not clinically linked to the other items within the scale.
Keywords: Clinical High-Risk States for Psychosis, Attenuated Psychosis Syndrome, Negative Symptoms, Factor Analysis

S240. Intact Motor Plasticity in Schizophrenia as Assessed by Transcranial Magnetic Stimulation With Paired Associative Stimulation

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Background: Deficient synaptic plasticity, including deficits in long term potentiation (LTP), may underlie impaired neurocognition in schizophrenia (SZ). LTP-like plasticity can be assessed non-invasively using the transcranial magnetic stimulation-paired associative stimulation (TMS-PAS) paradigm, involving repeated pairings of median nerve stimulation with a TMS pulse delivered over contralateral motor cortex.
Methods: SZ patients ($n=21$) and healthy controls (HC; $n=18$) underwent TMS-PAS with TMS intensity set to 120% of each subject's resting motor threshold (RMT). TMS-PAS comprised 240 TMS pulses at 0.25 Hz, with each pulse delivered 25 msec following median nerve stimulation with attention control. Electromyographic amplitude of the abductor pollicis brevis muscle (motor evoked potential; MEP) was recorded at baseline, 0, 15, 30, 45 and 60 minutes after TMS-PAS.
Results: The maximum MEP percent change was larger in SZ ($p=0.042$), although MEP potentiation was significant in both HC ($p<0.0001$) and SZ ($p<0.0001$). SZ patients showed smaller baseline MEP amplitudes ($p=0.001$), and smaller baseline MEPs were associated with larger MEP percent changes across groups ($p=0.030$). After covarying for baseline MEP, maximum percent change in MEP no longer differed between the groups ($p=0.670$).
Conclusions: TMS-PAS induced motor plasticity appeared intact in SZ at a TMS intensity of 120% RMT. This differs from prior findings of impaired plasticity in SZ at a TMS intensity required to produce a 1 millivolt MEP. Future studies are needed to investigate relationships between TMS intensity and motor plasticity in SZ.
Supported By: R21MH102727-01
Keywords: TMS, Schizophrenia, Neuroplasticity, Paired Associative Stimulation

S241. Investigation of Mechanism of Increased Appetite After Olanzapine by sLORETA During Sleep

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Background: Increased appetite is a frequent side effect of atypical antipsychotics like olanzapine and results in weight gain and an elevated risk of somatic disorders. The underlying mechanisms are widely unknown. The subgenual anterior singular cortex (sgACC) participates in regulation of appetite and sleep. Standardized low resolution brain electromagnetic tomography (sLORETA) related to sleep electroencephalogram (EEG) was used to test whether sgACC activity is influenced by olanzapine in healthy subjects. sLORETA is an EEG-based neuroimaging technique performing the inverse solution to quantify regional brain activity within predefined voxels.
Methods: 10 healthy, young male subjects underwent two 118 channel sleep-EEG recordings at baseline and after treatment with olanzapine up to 10 mg for 7 days. We used artifact-free 5 min EEG clips from the first N3-sleep period for the EEG bands for various frequency bands including α (8-12Hz). Appetite was assessed daily by self-rated questionnaire.
Results: In sgACC the current source density of α frequency band increased significantly after olanzapine from (mean$\pm$ S.E.M) 5.42 $\pm$ 0.128 to 5.76 $\pm$ 0.184 ($p > 0.005$). Sleep stage N3 increased from (mean $\pm$ SD) 17.3$\pm$ 5.93 % to 26.33 $\pm$ 10.45 % ($p = 0.00033$) and self-rated appetite increased from 59.33 $\pm$18.46% to 70 $\pm$17% ($p= 0.0015$).
Conclusions: Our findings suggest that changed activity in the sgACC participates in the increase of appetite after olanzapine. Furthermore, the capacity of sLORETA during sleep to investigate pharmacologic modulation of deep brain activity is demonstrated. The increases of sleep stage N3 and of appetite after olanzapine areas expected.
Keywords: Olanzapine, Appetite Regulation, sLORETA, Sleep, sgACC

S242. Do Long-Acting Injectable Antipsychotics Reduce Readmission Rates to Acute Inpatient Psychiatric Hospitals?

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Background: Prior studies have suggested that long-acting injectable (LAI) antipsychotics may be associated with lower rehospitalization rates than oral antipsychotics. The current study examined the impact of 2 of our most commonly used LAI antipsychotics versus their oral formulations in psychiatric inpatients admitted to an acute, inner-city, academic psychiatric hospital.
Methods: Patients (n=3240) admitted between January 1, 2010 and September 30, 2016 with a primary diagnosis of a Schizophrenia Spectrum Disorder and discharged on oral haloperidol (HL), haloperidol decanoate (HLD), oral fluphenazine (FL), and/or fluphenazine decanoate (FLD) were included in the study. The primary outcome measure was readmission within 30 days. We estimated odds of readmission by fitting a logistic regression model. In the multivariate model, we examined the differential effects of HL, HLD, FL, and FLD, controlling for demographic characteristics.
Results: Compared to patients discharged on HLD, patients discharged on FL (aOR=4.621, $p<0.001$), FLD (aOR=4.940, $p<0.001$), or HL (aOR=2.573, $p<0.001$) were more likely to be readmitted within 30 days when controlling for age, sex, and race. Additionally, younger age (aOR=.984, p=0.001), male gender (aOR=1.374, p=0.024), and white patients as compared to African-American (aOR=1.319, p=0.039) or other race (aOR=.475, p=0.019), were associated with a greater risk of 30-day re-admission.
Conclusions: These results suggest that HLD was more effective than HL in reducing rapid re-admission in patients with Schizophrenia Spectrum Disorders. If replicated, these findings provide further support that HLD may convey better outcomes than HL or FL in patients with chronic mental illness.
Keywords: Long-Acting Injection, Antipsychotics, Schizophrenia Spectrum, Readmission, Psychopharmacological Treatment

S243. Heightened Effect of Unfairness and no Effect of Oxytocin on Ultimatum Game Behavior in Schizophrenia

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Background: Social decision-making deficits are common and negatively impact functioning in schizophrenia. Understanding of these complex deficits is limited and treatments are unfortunately lacking. Oxytocin improves some social deficits in schizophrenia, but its effects on social decision-making remain unknown.
Methods: The Ultimatum Game (UG) quantifies preferences for monetary gains versus fairness norms and has been used to investigate social decision-making. To better characterize social decision-making deficits in schizophrenia and determine whether oxytocin can improve them, individuals with schizophrenia (n=40, SZ) and matched healthy controls (n=63, HC) played the UG after receiving a dose of intranasal oxytocin (40IU) and placebo in a randomized, double-blind, crossover study. We analyzed behavior using non-parametric tests.
Results: After receiving placebo, SZ rejected fair offers similarly to HC but rejected unfair offers more often than HC, regardless of whether the proposer had no choice (p=0.003) or was intentionally unfair (p=0.008). SZ and HC were equally responsive to the intention behind offers, i.e. both groups rejected unfair offers more often when the proposer could have offered a fair split. Oxytocin administration did not impact rejection behavior in either group for any condition.
Conclusions: Our results suggest that schizophrenia is associated with an intact preference for fairness, but a heightened response to unfairness. This implies that social norm violations may be more aversive in SZ. Further experiments are needed to elucidate the mechanisms underlying this behavior. Oxytocin did not impact the aspects of social

decision-making captured by the UG and is thus unlikely to effectively treat deficits in this area.
Supported By: Veteran's Affairs Office Career Development Award - Josh Woolley (PI)
Keywords: Schizophrenia, Oxytocin, Cognitive/Decision Processes

S244. Potent Dopamine D2 Receptor Antagonists Block the Reward-Enhancing Effects of Nicotine in Smokers With Schizophrenia

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Background: Mesolimbic dopamine reward system dysfunction has been hypothesized to contribute to high rates of smoking in schizophrenia, given that nicotine transiently improves reward function by stimulating dopamine release. Since activation of dopamine D2 receptors has been found to mediate motivation for nicotine, we examined whether antipsychotics with potent D2 antagonism moderated the reward-enhancing effects of smoking in schizophrenia.
Methods: Chronic smokers with schizophrenia (n=114) were stratified into groups based on D2 antagonist medication potency and completed a probabilistic reward task (PRT) before and after smoking a cigarette. The PRT used an asymmetrical reinforcement schedule to produce a behavioral response bias, which has been found to increase under conditions (including smoking) that enhance phasic striatal dopaminergic signaling.
Results: Ninety-eight subjects had usable data. A D2 Antagonist Potency x Smoking x Block interaction emerged, $F(1,96)=8.17$, $p=.005$, $np2=.08$. Examination of the Smoking x Block interaction within each D2 antagonist group revealed a significant interaction only for those taking weaker D2 antagonists, $F(1,27)=7.57$, $p=.01$, $np2=.22$. Within this group we observed a smoking-related enhancement in response bias across blocks of the task ($p<.001$) that was absent in those taking potent D2 antagonists ($p>.05$).
Conclusions: These data suggest that antipsychotics with potent D2 antagonist profiles diminish the reward-enhancing effects of nicotine in smokers with schizophrenia. This may drive increased rates of smoking, as more nicotine may be needed to achieve the same level of striatal D2 stimulation. The clinical implications for treating nicotine dependence in patients medicated with potent D2 antagonists will be discussed.
Supported By: National Cancer Institute
Keywords: Schizophrenia, Nicotine Dependence, Reward Responsiveness, Dopaminergic Signalling, Antipsychotics

S245. A Systematic Review and Meta-Analysis of Pharmacological Interventions for Reduction or Prevention of Weight Gain in Schizophrenia

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Background: Weight gain is an extremely common problem in schizophrenia patients and is associated with morbidity and mortality. We conducted a Cochrane meta-analysis to determine the effects of pharmacological interventions aimed at reduction or prevention of weight gain in schizophrenia.
Methods: We searched the Cochrane Schizophrenia Group's Trials Register and registries of clinical trials. All double blind randomized controlled trials examining any adjunctive pharmacological intervention for weight loss (treatment) or weight maintenance (prevention) in patients with schizophrenia or schizophrenia-like illnesses were included. The primary outcome measure was weight loss.
Results: Forty-four randomized controlled trials met the inclusion criteria. Nine studies examined prevention of antipsychotic-induced weight gain. Reboxetine may be slightly effective in preventing weight gain (MD = -2.09 kg, 111 participants; 3 studies) but the quality of evidence is low.

Thirty-five studies examined reduction of weight gain. Metformin causes modest weight loss (MD = -3.36 kg, 601 participants, 9 studies). First episode psychosis patients appeared to benefit most from early intervention with metformin. Treatment with metformin may cause additional adaptive changes in fasting insulin levels and insulin resistance. Quality of evidence for other agents is low. None of the adjunctive treatment strategies resulted in higher dropout rates.
Conclusions: Accumulating evidence supports the safe use of pharmacological interventions to achieve modest weight loss. Reboxetine may be slightly effective in preventing weight gain while metformin has the most evidence for use as treatment of weight gain. The small number of studies, small sample size, and short study duration limits interpretation for other agents.
Keywords: Schizophrenia, Weight Gain, Pharmacology, Treatment, Meta-Analysis

S246. Psychosis in a Patient With Retinitis Pigmentosa: Beware of D4 Receptor Blockade!

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Background: Retinitis Pigmentosa is a rare inherited degenerative disease affecting the retinal pigment epithelium. While Dopamine 2 (D2) receptor blockade remains the sine qua non of antipsychotic activity, the D2 family also includes D3 and D4 receptors. Most atypical antipsychotics have high affinity for the D4 receptors abundant within the rods of the retina and dopamine release is the primary feedback mechanism preventing retinal degeneration by the unopposed action of melatonin. With these issues in mind, the current case discusses the selection of an antipsychotic in the context of retinitis pigmentosa.
Methods: 50-year-old female with Schizophrenia and Retinitis Pigmentosa was admitted to our academic inpatient unit

for acute psychotic exacerbation with agitation and persecutory delusions. She initially refused taking any antipsychotics due to her belief that the medication would further exacerbate her legally blind condition. Since she remained very psychotic, a petition for forced medication administration was filed and subsequently approved by the mental health court.
Results: Quetiapine and Abilify have a relatively low affinity for the D4 receptor, but no IM and/or depot formulations were available at the inpatient facility. Haloperidol, available in IM and depot formulations, was selected based on its similar D4 affinity to the remaining atypical antipsychotics. Patient eventually became med compliant with good treatment response and tolerability including no change in visual acuity.
Conclusions: Treatment in such patients requires consideration of the potential D4 receptor effects associated with antipsychotics. Since there is little data available concerning this rare but important issue, this case report provides some guidelines for management.
Keywords: Acute Psychosis, Dopamine, Melatonin, Antipsychotics

S247. Therapeutic Efficacy of Atypical Antipsychotic Drugs by Targeting Multiple Stress-Related Metabolic Pathways in Schizophrenia Patients

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Background: In the animal models, we have revealed the efficacy of atypical antipsychotic drugs (AAPDs) by targeting multiple stress-related metabolic pathways reflected by a panel of biomarkers (Cai et al. Transl Psychiatry. 2017, 7(5):e1130.). Herein, we aim to further validate these stress-induced biomarkers in schizophrenia patients.
Methods: The fasting plasma samples were collected from a total of 147 first-episode antipsychotic-naïve (FEAN-SZ) or relapsed antipsychotic-free schizophrenia inpatients at baseline and after 4 weeks of AAPD treatment, and from 74 gender- and age-matched healthy controls. A UFLC-MS/MS method was developed to quantify the panel of stress-induced biomarkers simultaneously. The SIMCA-P v12.0 was used for multivariate analyses of metabolic profile changes.
Results: The primary findings were as follows: (1) at baseline, the plasma levels of choline, allantoic acid, corticosterone, cortisol and lysophosphatidylcholines (LysoPC16:0; 18:1; 18:0) were increased, while hypoxanthine, uric acid, inosine, progesterone and phosphatidylethanolamines (PE16:0/22:6; 18:0/22:6) were decreased in schizophrenia patients; (2) following a 4-week AAPD treatment, the concentrations of creatine, inosine and PEs were elevated and that of cortisol was reduced, in which FEAN-SZ showed greater responsiveness; (3) the metabolic profiles of healthy controls, schizophrenia patients at onset (baseline) and remission stages (4-week) were clearly separated in the scores plot of PLS-DA model, which can classify and discriminate the subjects with a high accuracy of 95.9%.
Conclusions: The biomarker changes suggest the deficits of energy and purine metabolism, excessive membrane phospholipid breakdown and disrupted neurosteroidogenesis in schizophrenia patients. The panel of stress-induced biomarkers is state-like and may potentially serve for therapeutic monitoring in schizophrenia patients.
Supported By: Nature Science Foundation of China [NSFC81401113 (HLC)], the Specialized Research Fund for the Doctoral Program of Higher Education of China [SRFDP20130162120060 (HLC)], and Hunan Provincial Natural Science Foundation of China [2017JJ3444 (HLC)]
Keywords: Atypical Antipsychotic Drug, Schizophrenia, Stress, Metabolomics, Biomarker

S248. Resting State Functional Connectivity From Hippocampus and Nucleus Accumbens Correlates With Symptom Dimensions in Schizophrenia

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Background: Cerebral dysconnectivity is thought to contribute to the schizophrenia syndrome phenotype. Reward system dysfunction was reported in schizophrenia. Here we test, whether resting state connectivity from the reward system would be linked to reward-related schizophrenia symptoms, such as delusions or avolition.
Methods: 46 schizophrenia patients underwent resting state fMRI scans at 3 T for 8 mins. Using the CONN toolbox, we tested the connectivity from bilateral seeds of hippocampus and nucleus accumbens (NACC). Results were family-wise-error corrected. Partial correlations were computed correcting for antipsychotic medication dosage between the extracted connectivity values from seeds to the resulting clusters and related symptom scores: DSM-5 symptom severity ratings of delusions and SANS avolition scores.
Results: Seed-to-voxel analyses indicated that left hippocampus and bilateral NACC had three clusters, while right hippocampus had 6 clusters with significant covariance at rest. SANS avolition scores correlated with connectivity between right NACC-left temporal pole cluster ($r = -.30$, $p = .04$), and with connectivity between left hippocampus-left sensorimotor cortex ($r = .36$, $p = .01$). Delusion severity was linked to connectivity between left hippocampus and a large cluster of bilateral frontal cortex and basal ganglia ($r = .43$, $p = .003$), as well as to connectivity from left NACC to left mesial temporal cortex ($r = .41$, $p = .005$).
Conclusions: Aberrant functional connectivity at rest from the reward system seeds is associated with severity of delusions and avolition. Findings argue for specific associations between network dysfunction and distinct symptom dimensions in schizophrenia.
Supported By: Swiss National Science Foundation
Keywords: Resting State Functional Connectivity, Nucleus Accumbens, Hippocampus, Delusions, Apathy

S249. L-DOPA Induces Psychosis-Like Perception by Disrupting the Discrimination Between Relevant and Irrelevant Stimuli

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Background: Psychotic symptoms such as delusions and hallucinations are profound alterations of how the world is perceived, and have been consistently linked to excessive dopaminergic neurotransmission. However, the mechanisms by which increased dopamine induces perceptual alterations characteristic for psychosis have remained elusive. Here, we asked whether pharmacological dopaminergic stimulation leads to psychosis-like alterations by an overall increased bias to perceive sensory information as relevant or, alternatively, by an impaired ability to discriminate between relevant and irrelevant information.
Methods: 24 healthy individuals received 150mg L-DOPA in a double-blind, balanced, placebo-controlled, within-subject design, and participated in two visual perception tasks. In the first task, participants had to discriminate direct versus averted gaze, which we used to quantify the psychosis-like misperception of being looked at. In the second task, participants had to discriminate faces embedded in noise versus pure noise which we used to measure the psychosis-like misperception of meaning in noise. Data were analyzed according to signal detection theory.
Results: For both tasks, there was no significant drug effect on bias ($p = 0.617$ and $p=0.094$) but a marked decrease of discriminability under L-DOPA compared to placebo ($p=0.009$ and $p=0.049$). Hence, under L-DOPA, participants felt more frequently looked at by averted gaze and more frequently detected faces in pure noise. At the same time, under L-DOPA, participants more frequently missed direct gaze or faces embedded in noise.
Conclusions: Increasing dopaminergic neurotransmission enhances psychosis-like perception by disrupting the discrimination between relevant and irrelevant stimuli rather than by inducing a bias to perceive stimuli as relevant.
Supported By: BMBF (German Federal Ministry of Research and Education)
Keywords: Dopamine, Delusions, Hallucinations, Perception, Model Psychosis

S250. Associations Between Contrast Processes and Resting-State Functional Connectivity in Patients With Schizophrenia and Healthy Controls

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Background: People with schizophrenia exhibit visual deficits including impaired ability to process contrast. The associations between psychophysically-assessed visual contrast sensitivity (CS) and within-network functional connectivity (coherent fluctuations of low-frequency fMRI signals during resting state) were examined in schizophrenia.
Methods: Thirty-seven patients with schizophrenia or schizoaffective disorder and 38 healthy controls completed a psychophysical CS task using stimulus gratings of low (0.5, 1 cycles/degree) and high (4, 7, 21 cycles/degree) spatial frequencies and underwent resting-state fMRI. Functional connectivity was obtained within seven networks: visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode. Independent-samples t-test examined group differences in CS. Pearson correlations were computed between measures of CS and functional connectivity in these networks.
Results: Patients showed reduced CS compared to controls ($p < .001$). There were no significant correlations between CS and any of the functional connectivity networks for patients (ps $> .05$). However, healthy controls showed significant positive correlations between CS at low spatial frequencies and the dorsal attention ($r = .37$) and frontoparietal network ($r = .45$) and between CS at high spatial frequencies and the somatomotor ($r = .38$), dorsal attention ($r = .42$), ventral attention ($r = .49$), limbic ($r = .34$), frontoparietal ($r = .51$), and default mode networks ($r = .43$) (ps $< .05$).
Conclusions: These exploratory findings indicate that contrast processing is related to network-level functional connectivity throughout the brain for healthy individuals, with high spatial frequency processing potentially related to more global secondary processing. These relationships were lacking in schizophrenia.
Supported By: National Institutes of Health Grants R01-MH66374, R01MH64783, and R21MH084031
Keywords: Schizophrenia, Visual Processing, Functional Connectivity, Contrast Sensitivity, Resting State fMRI

S251. The DAT1 3' VNTR is Associated With a Reward Deficiency Phenotype in a Study of Sexual Addiction

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Background: Guo et al. (2007) reported that men with at least one 10-repeat allele of the DAT1 3' VNTR had an 80-100% increase in number of partners compared to those with two 9-repeat alleles.
Methods: Our study aims to include 500 individuals with sexual addiction, and 1500 controls. To date 292 individuals seeking treatment for sexual addiction and 1011 volunteers from which the control population will be drawn have been recruited and passed through at least one phase of the study. Cases of sexual addiction have been defined using the 20 core

items of the Sexual Addiction Screening Test – Revised (SAST-R): a score of at least 11 in those seeking treatment, or a score of at least 6 in the volunteers. The DAT1 3' VNTR has been genotyped for 535 total (235 cases by the SAST-R definition, 500 controls) using the method as described by Vandenberg et.al (1992).
Results: In the 235 cases, the frequency of the DAT1 3' VNTR 8, 9, 10, and 11 repeat alleles was 0.004, 0.238, 0.743, and 0.015 respectively. The 129 controls defined as above, the frequency of DAT1 3' VNTR was 0.004, 0.229, 0.764, and 0.004. There was a nominally significant difference in the genotypic distribution of the cases versus controls ($p=0.048$), with a similar difference being seen between those defined as positive for a reward deficiency phenotype versus controls ($p=0.049$).
Conclusions: In this interim analysis, consistent with prior data, the DAT1 3' VNTR appears to be associated with a reward deficiency phenotype.
Supported By: Fulbright Canada and the Palix Foundation (Distinguished Scholar award to PC), the American Foundation for Addiction Research and the Government of Alberta (Alberta Centennial Addiction and Mental Health Research Chair transitional funding to KJA).
Keywords: Addiction, Sex, Internet Addiction, ADHD, Psychiatric Genetics

S252. Fronto-Temporo-Occipital Cortical Thickness Measures Predict Poor Sleep Quality in At-Risk Youth

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Background: Poor subjective sleep quality (SQ) is a prominent risk factor for most forms of psychiatric illness, yet objective biomarkers of SQ have remained elusive. Our goal was to identify neural markers of SQ in at-risk youth using a combination of structural and functional neuroimaging assessments.
Methods: A transdiagnostic sample of 40 youth (8-17yr) completed an MRI assessment and rated past-week SQ with a modified Pittsburgh Sleep Quality Index (N=22 good SQ [PSQI≤5]; N=18 poor SQ [PSQI>5]). Group-lasso logistic regression identified non-zero predictors of SQ from cortical thickness measures; BOLD response to reward and emotion fMRI tasks; and demographic/clinical features.
Results: Poor SQ was associated with higher depression severity and cortical thickness in sensory regions (thinner right superior temporal sulcus and left temporal pole, thicker right lateral occipital cortex). Age interacted with right superior frontal[SFC] cortical thickness to predict SQ, such that SFC thickness and age were positively associated in youth with good SQ and negatively related in those with poor SQ. Anxiety severity interacted with right rostral anterior cingulate[rACC] cortical thickness to predict SQ, such that rACC thickness and anxiety were negatively related in youth with good SQ and positively related among youth with poor SQ. Predictors explained 51.2% of the variance in SQ and correctly classified 85% of cases.
Conclusions: Age, internalizing symptoms, and cortical thickness in sensory and frontal midline regions, were useful classifiers of SQ. A combination of measures may be necessary to understand the neural basis of poor SQ and its role in psychiatric illness.
Supported By: R01MH060952; K01MH111953
Keywords: Sleep, Cortical Thickness, Task fMRI, Transdiagnostic, Youth

S253. Sleep Disturbances, Disruption of Circadian Rhythm and Loss of Daily Melatonin Secretion in CAF Military Personnel Suffering From Post-Traumatic Stress Disorder

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Background: According to DSM-5, sleep disturbance is a core feature of PTSD. About 70% of individuals with PTSD have co-occurring sleep problems, reporting greater trouble initiating and maintaining sleep. Melatonin is secreted by the pineal gland during physiologic night, synchronizing circadian timing and regulating sleep–wake cycle. This prospective investigation examined sleep characteristics and nocturnal melatonin production in military PTSD sufferers with endorsed sleep difficulties.
Methods: Volunteers included seven treatment-seeking Canadian Armed Forces (CAF) members, aged 31–45 years, with a diagnosis of PTSD under DSM-5 criteria, including CAPS≥50. Healthy CAF members with no history of PTSD or sleep disorders served as controls. Participants wore wrist actigraphy during sleep for 7-days to derive estimates of sleep quality/quantity (total sleep time [TST], sleep latency [SLAT], wake after sleep onset [WASO], sleep efficiency [SE]). On day-8, participants remained in dim-light (<5 lux) for 24 h, during which saliva was sampled bi-hourly to measure endogenous melatonin levels (ELISA, pg/ml) and assess dim-light melatonin onset (DLMO).
Results: PTSD patients exhibited significant sleep disturbances, with lower (mean±SD, min) TST (385.6±64.1), greater SLA (12.8±12.1) and WASO (51.4±25.1), with an increased number of awakenings (17.8±9.1) and poor SE compared to healthy controls. Peak salivary melatonin levels in PTSD patients averaged 2.6±1.1 (range=1.4–4.7) over 24-h, relative to controls (range=20–100). Melatonin production was insufficient to calculate a DLMO in PTSD patients.
Conclusions: Our findings support research linking variable sleep patterns and circadian disruption to PTSD pathogenesis, suggesting chronodisruption may play a causal role in development of PTSD symptoms. Further preclinical and clinical studies are needed.

Supported By: Defense Research & Development Canada
Keywords: Sleep Disorders, Melatonin, PTSD - Post-traumatic Stress Disorder, Circadian Rhythms, Military Combat Soldiers

S254. Beyond Pain in Fibromyalgia: Limbic Related EEG-Neurofeedback Training Improves Sleep and Affect

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Background: Fibromyalgia (FM) is a chronic pain syndrome where somatic and affective dimensions are entangled. This mind-body interaction manifests, beyond pain, in disordered sleep and emotion dysregulation. It has been argued that FM chronicity stems from abnormal function of limbic areas, such as the amygdala. Yet, it is unclear to what extent limbic abnormality underlies the different dimensions of FM. To address this, we employed a novel fMRI-inspired EEG-neurofeedback (NF) (Amygdala Electrical Finger Print (Amyg-EFP)) in FM patients, targeting deep limbic structures. We expected that successful NF learning will impact affective more than somatic related dimensions.
Methods: 34 FM patients (31F; Age 35.6±11.82) underwent 8-10 NF sessions, with nine patients randomly assigned to perform sham NF and used as controls. Self-report of pain, depression, anxiety and sleep quality as well as objective sleep measures were collected before and after the NF course.
Results: Subjective measures of depression, anxiety and sleep, but not pain, improved in correlation to NF-learning index, with high learners (n=13/25) displaying remarkably stronger correlation than low learners (depression/anxiety: R=0.673; p=0.016, sleep quality R=0.618, p=0.032). REM latency, a somatic marker for depressive mood, was improved only in the test group ($F(1,30) = 4.43$; $p < 0.05$), more so in high learners ($F(2,29) = 4.46$; $p < 0.05$).
Conclusions: These results show that Amyg-EFP-NF, may impact homeostatic processes related to sleep and affect in FM. Hence, limbic dysregulation involves in FM chronic manifestations, possibly with long-term impact on pain.
Supported By: The Israel Innovation Authority- The KAMIN incentive program
Keywords: Amygdala, Neurofeedback, Sleep Disorders, Affective Disorders, Chronic Pain

S255. Investigation of the Possible Reinforcing Effects of Samidorphan and Naltrexone by Fixed and Progressive Ratio Intravenous Self Administration Testing in Rats

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Background: Samidorphan is a μ-opioid receptor antagonist being developed in combination with buprenorphine (ALKS 5461) and olanzapine (ALKS 3831). We investigated whether samidorphan or naltrexone served as positive reinforcers in rats trained to self-administer heroin.
Methods: Male Sprague Dawley rats (N=7-8/group) trained to self-administer heroin followed by saline extinction were divided into 3 groups: heroin, samidorphan or naltrexone. Training and testing were on FR5 (2hr sessions). When stable self-administration was observed, break point was determined (4hr PR session).
Results: Samidorphan was not a reinforcer at 13.6 or 40.8μg/kg/inj, however 68μg/kg/inj was significantly greater than saline (9.2±2.1 vs. 4.3±0.2, respectively, $p<0.01$). All samidorphan break points were significantly lower than heroin ($p<0.01$). Break-points for the 2 lower doses of samidorphan were not significantly different from saline, however the high dose was ($p<0.05$).

No doses of naltrexone were reinforcing; however, the low dose almost reached significance (p=0.053). Break points were not significantly different from saline and all significantly lower than heroin.

There were no differences when FR5 and PR/break-point results for samidorphan were compared to naltrexone.
Conclusions: Samidorphan elicited a weak signal as positive reinforcer at one dose. An equivocal reinforcement signal was observed for naltrexone. Break-points for samidorphan were not significantly different from those of naltrexone, which has no abuse liability, and significantly lower than heroin. Overall the profiles of samidorphan and naltrexone were similar in this model.
Supported By: Alkermes, Inc
Keywords: Abuse Potential, Self-administration, Antagonist, Opioid System

S256. Long-Noncoding Rna Gas5 is Associated With Cocaine Action

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Background: Long non-coding RNAs (lncRNAs) are a class of transcribed RNA molecules greater than 200 nucleotides long that do not encode proteins. Recently, many lncRNAs have been recognized to be functionally important, particularly with respect to the regulation of gene expression. Though lncRNAs are abundant in the brain, their neural functions are largely unknown.
Methods: Here we examine the expression of lncRNA growth arrest-specific 5 (Gas5) in the mouse nucleus accumbens (NAc) both 1 and 24 hours after 7 daily cocaine intraperitoneal (i.p.) injections, as well as 10 days after 28 days of cocaine i.p. administration. We also evaluate its behavioral functions in cocaine action through viral over-expressions.
Results: We found Gas5 is constantly downregulated at all time points studied. Though Gas5's neural function is unclear, accumulating evidence suggests that Gas5 may prevent glucocorticoid receptor from interacting with the glucocorticoid response element, and thereby suppresses glucocorticoid downstream nuclear signaling. In order to elucidate the role of Gas5 in cocaine action, we performed viral over-expression of Gas5 in mouse nucleus accumbens. We found Gas5 significantly decreases cocaine preference and administration.
Conclusions: As glucocorticoid receptor is implicated in drug addiction, further study of long non-coding RNA Gas5 may provide a novel molecular underpinning of drug addiction.
Supported By: NIDA
Keywords: Addiction, Epigenetics, gas5, Glucocorticoid, Long Non-Coding RNA

S257. Whole Epigenome Analysis and Replication Implicates PCSK9 in Alcohol Use Disorder

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Background: Alcohol Use Disorder (AUD) is a common and chronic disorder with substantial effects on personal and public health. The underlying pathophysiology is poorly understood but strong evidence suggests significant roles of both genetic and epigenetic components.
Methods: Cross-tissue and cross-phenotypic analysis of genome-wide methylomic variation using Illumina HM450 and EPIC chip arrays in AUD samples from 3 discovery, 4 replication, and 2 translational cohorts was performed. The discovery samples consisted of postmortem brain tissues (n=46), bloods form a resting-state functional connectivity imaging endophenotypes (n=68) and postmortem brain tissues sorted into neuronal and non-neuronal cells (n=58).
Results: Overrepresentation analyses identified 68 significant CpG probes of which the most significantly associated probe cg01444643 was in in the promoter of the proprotein convertase subtilisin/kexin 9 (PCSK9) gene ($p=0.002$). Biological validation showed that PCSK9 promoter methylation is conserved across tissues and positively correlated with expression. Replication in AUD datasets confirmed PCSK9 hypomethylation (n=392, $p<0.05$) and a translational mouse model of AUD showed that alcohol exposure leads to PCSK9 mRNA and protein downregulation ($p<0.0001$). Postmortem human liver tissue analyses in control (n=47) and liver transplant cases due to alcohol cirrhosis (n=50) showed increase of methylation at cg01444643 ($P<0.0001$) and decreased PCSK9 expression ($p<0.01$). PCSK9 is primarily expressed in the liver and regulates low density lipoprotein cholesterol.
Conclusions: Our finding of alcohol-induced epigenetic regulation of PCSK9 represents one of the underlying mechanisms between the well-known effects of alcohol on lipid metabolism and cardiovascular risk, with light alcohol use generally being protective while chronic heavy use has detrimental health outcomes.
Supported By: NIAAA intramural program
Keywords: Epigenetic, Lipids, Cholesterol, Genetics, DNA Methylation

S258. Dorsal, but Not Ventral Striatal Dopamine Mediates the Effect of Gambling Disorder on Compulsivity During Reversal Learning

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Background: Gambling disorder is characterized by compulsive gambling. Besides playing an important role in addiction, dopamine – especially in the dorsal striatum – has also been implicated in compulsivity. Recently we found evidence for higher striatal dopamine synthesis capacity in individuals with gambling disorder compared with controls. Here we test the mediating role of dorsal striatum (DS) and ventral striatum (VS) dopamine synthesis capacity in compulsivity.
Methods: We quantified compulsivity in terms of perseverative errors during a probabilistic reversal learning paradigm and combined this with FDOPA-PET to measure dopamine synthesis capacity (Ki values) in 14 controls and 12 pathological gamblers. We employed mediation analyses (using Lavaan in R and bootstrapping (n=5000)), including diagnosis (gamblers versus controls) as a predictor, and DS or VS Ki values as mediators. Furthermore, we directly compared the mediating role of the DS versus VS on predicting these outcome measures.
Results: The mediation model with DS Ki values was significant: diagnosis predicted perseverative errors ($p<0.005$), diagnosis also predicted DS Ki values ($p<0.001$), which in turn predicted perseverative errors ($p<0.001$). In addition, the indirect effect of diagnosis on perseverative errors via DS Ki was significant ($p<0.007$). The same model with VS Ki values was not significant, and a direct comparison of the two models indicated a significant difference in the mediation effect of DS versus VS Ki values on perseverative errors ($p<0.015$).
Conclusions: Our mediation analyses indicate that dopamine synthesis capacity specifically in the DS, and not the VS

mediates the relationship between gambling disorder and compulsive, perseverative behavior.
Supported By: Dr van Holst was supported by a Rubicon grant from the Netherlands Research Organization (NWO, ref nr. 446.11.025). Dr Sescousse is supported by a Veni grant from the Netherlands Research Organization (NWO, ref nr. 016.155.218). Dr Jagust serves as a consultant to Genentech, Novartis, and Bioclinica. Dr Cools is supported by a VICI grant from the Netherlands Research Organization (NWO, ref nr. 2015/24762/MaGW) and a James McDonnell scholar award.
Keywords: Dopamine, Compulsivity, PET Imaging, Gambling Disorder, Reversal Learning

S259. Non-Invasive Brain Stimulation Modifies a Brain Network That Supports Abstinence During Alcohol Use Disorder Recovery

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Background: New interventions are needed to improve high relapse rates in alcohol use disorder (AUD). Our neuroimaging evidence has reported that individuals with AUD with long-term abstinence have higher resting functional connectivity (FC) between left dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAcc) than those with short-term abstinence. Low FC in this network during early abstinence predicts subsequent relapse. Brain FC can be enhanced with transcranial direct current stimulation (tDCS). This study aimed to investigate whether resting FC within a network known to mediate abstinence in AUD can be enhanced with tDCS and whether FC changes are related to treatment outcome.
Methods: We used a double-blind longitudinal study design. Intervention: 10 cognitive training sessions combined with either sham-tDCS or active-tDCS (anode: left DLPFC). Rest fMRI data was collected pre- and post-intervention. Six AUD subjects undergoing active-tDCS were compared to five AUD subjects undergoing sham-tDCS. We hypothesized that individuals assigned to receive stimulation would show increases in DLPFC-NAcc FC when compared to individuals assigned to receive sham-tDCS. Logistic regression analysis explored whether DLPFC-NAcc FC change can predict treatment outcome.
Results: Preliminary analyses examining DLPFC-NAcc FC revealed a significant Group x Time interaction FC ($F=7.105$, $p=0.026$). Only those assigned to active-tDCS showed DLPFC-NAcc FC increase across time. Logistic regression analysis revealed that treatment outcome could be predicted with 82% accuracy based on DLPFC-NAcc FC change ($p=.17$).
Conclusions: These pilot data suggest tDCS can improve prefrontal-striatal resting connectivity. Current findings can guide future neuromodulation interventions that combine cognitive training and brain stimulation to improve treatment outcomes.
Supported By: UL1TR000114
Keywords: Neuromodulation, Neuroplasticity, Alcohol Addiction, Neuroimaging, Resting State Functional Connectivity

S260. An Updated Report of Associations Between Cannabis Use and Brain Structure

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Background: Alongside support for legalization of medical and recreational cannabis, concerns remain about the effects of exogenous cannabis exposure on brain regions rich in cannabinoid receptors. Here we re-examine the relationship between cannabis use and brain structure in 1031 young adults with varying levels of cannabis use, controlling for confounding variables.
Methods: Participants were drawn from the 1200 Subject Release from the Human Connectome Project (HCP) public dataset. Brain volume and cortical thickness estimates were extracted using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). We ran a general linear mixed model, which was used to evaluate the significance of the effect of levels of cannabis use on each structure of the brain controlling for age, sex, alcohol consumption, cigarette use, and use of other illicit drugs. In order to account for heritability, zygosity and family structure were introduced in the model as random effects.
Results: After estimating effects from twin and sibling correlations, and controlling for alcohol, tobacco, other illicit drugs, age, and sex, 20 regions survived a Benjamini-Hochberg correction for multiple comparisons, and four regions survived a Bonferroni correction of $p<0.05$ divided by 82 ($p < 0.0006$). Those four regions were: left hippocampus volume, and cortical thickness of the right entorhinal cortex, temporal pole, and lateral occipital cortex.
Conclusions: This report is the largest and most comprehensive dataset to assess associations between cannabis use and brain structure controlling for confounding factors. Hippocampal volume reductions, as well as cortical thickness reductions in the medial temporal lobe, may contribute to potential associations between cannabis use and memory.
Supported By: K01DA034093
Keywords: Cannabis, Structural Neuroimaging, Human Connectome Project

S261. Emotion Recognition and its Relation to Prefrontal Function and Network in Heroin Plus Nicotine Dependence: A Pilot and Translational Study

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Background: Many patients with substance use disorders (SUDs) live in a stressful environment, and comorbidity is not uncommon. Understanding the neural mechanisms underlying heroin and nicotine dependences and their relationships to social cognition could facilitate behavioral therapy efficacy. We

aimed to provide a translational approach that leads to identifying potential biomarkers for opioid use disorder (OUD) susceptibility during recovery. We examined the clinical characters and the relationships between Theory of Mind (ToM) and executive functions (EF) in 3 groups: heroin plus nicotine dependent (HND) patients who had remained heroin abstinent ($\geq$ 3 months), nicotine dependent (ND) subjects and healthy controls (C).
Methods: The domains included emotion recognition, inhibition, shifting, updating, access, and processing speed. Resting state functional connectivity (rsFC), task-induced functional connectivity, and brain networks were then explored among 21 matched subjects using functional near infrared spectroscopy.
Results: HND enhanced the severities of anxiety, depression, and hyperactivity. Inhibition was impaired in both HND and ND. No impairment in domains of emotion recognition, access, and update was observed. HND demonstrated enhanced rsFC in the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC), and decreased ToM-induced connectivity across the PFC. The right superior frontal gyrus in the OFC (oSFG; $x = 22$, $y = 77$, $z = 6$) was associated with working memory and emotion recognition in HND.
Conclusions: Using a novel neuroimaging tool, these results supported the prominent reward-deficit-and-stress-surfeit hypothesis in SUDs, especially OUD, after protracted withdrawal. This may provide an insight in identifying potential biomarkers related to a dynamic environment.
Supported By: Other
Keywords: Opiate Addiction, fNIRS, Graph Theory, Resting-State Functional Connectivity, Tabaco

S262. Novel Targeted Clathrin-Based Superparamagnetic Iron Oxide Nanoparticles for CNS Magnetic Resonance Imaging of Dopamine Transporters

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Background: Magnetic Resonance Imaging (MRI) offers high spatial resolution, but has poor sensitivity for visualization of molecular targets. Superparamagnetic iron oxide (SPIO) contrast agents along with antibodies are used to improve MRI sensitivity and molecular targeting, but they cannot cross an intact blood-brain-barrier (BBB), limiting their use. Our goal was to enable MR molecular imaging of dopamine transporters (DAT) using novel clathrin-based nanoprobes carrying SPIO and anti-DAT-antibodies, which noninvasively pass an intact BBB.
Methods: Clathrin triskelia (CT)-nanoprobes were synthesized by conjugating anti-DAT-antibody and SPIO to CT using polyethylene glycol at 1:1:1 molar ratio. Adult male mice were given saline or CT-nanoprobes intranasally (68 pmol, 50 μL). 4 hours later, their brains were perfused, fixed, and collected for immunohistochemistry or ex-vivo MRI. Voxel-wise R2* relaxation rates were obtained using a series of gradient-echo images, and estimated in the striatum (STR) and visual cortex (vCTX, a control region).
Results: The iron stained brain slices showed an accumulation of CT-nanoprobes in brain regions rich in DAT (e.g., STR). MRI studies revealed that R2* values were significantly higher in the STR than vCTX ($p=0.0051$) in animals that received CT-nanoprobes, but not in saline treated animals. CT-nanoprobes significantly increased R2* in the STR compared to saline ($p=0.0002$) without significantly altering R2* in vCTX.
Conclusions: CT-nanoprobes noninvasively delivered SPIO contrast agents along with anti-DAT-antibody to the mouse brain, enabling detection of DAT using MRI. These preliminary results merit further investigation into the use of clathrin as a new theranostic for noninvasive molecular brain imaging and targeted drug delivery.
Supported By: K08DA037465, R43DA044050, T32DA015036
Keywords: Brain Magnetic Resonance Imaging (MRI), Dopamine Transporter Imaging, Clathrin Nanoparticles, Superparamagnetic Iron Oxide (SPIO), Dopamine Transporter Antibody

S263. The Association Between Age of Onset and Total Lifetime Use of Marijuana With Hippocampal Volume in Adolescents

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Background: Marijuana (MJ) is the most commonly used illicit substance in the United States, especially in adolescent populations. A number of previous investigations have suggested a negative relationship between MJ use and brain development. This study looked at the relationship between age of onset and total lifetime use and hippocampal volume of MJ users.
Methods: Fifty-one MJ using adolescents and forty healthy controls were included in this study. All participants were males between 13 and 24 years of age. Structural brain images were acquired with T-1 weighted 3D MPRAGE sequence on a 3T Trio scanner. Structural MRI was analyzed using FreeSurfer software to acquire regional brain volumes.
Results: No between group differences were found between MJ and HC groups in regard to hippocampal volumes. However, the right hippocampus correlated with age of onset ($r=.290$, $p=.039$) in the MJ group. Moreover, there were significant correlations between right parahippocampal volume and age of onset ($r=.378$, $p=.006$), and total lifetime use ($r=-.380$, .006). There were no significant correlations found between age of onset or lifetime use and the left hippocampus or left parahippocampus.
Conclusions: Results show that hippocampal volume is associated with age of first use and total lifetime use in MJ using adolescents. These findings extend results from previous studies that have shown changes in hippocampal volumes in individuals with a history of MJ use by demonstrating an association with age of onset and total lifetime use. Additional studies are needed to clarify if the observed associations are the results of MJ use.
Supported By: 1R01 DA020269-01
Keywords: Marijuana, Adolescence, Substance Use, Imaging

S264. Association Between Caudate Volume and Sensation Seeking Behavior in Marijuana Using Adolescents

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Background: Marijuana (MJ) has been associated with behavioral changes as well as structural and functional alterations in the brain. Studies have suggested that increased sensation seeking behavior (SSB) is a risk factor for the initiation and use of various substances including marijuana. Differences in SSB have also been associated with reward processing in the brain. Therefore, we hypothesized that adolescent MJ users would exhibit increased SSB, which would be correlated with subcortical brain regions associated with reward processing.
Methods: Twenty-two MJ-using and 19 healthy adolescents (HC) completed clinical measures including all four subscales of the Sensation Seeking Scale (SSS) and magnetic resonance imaging (MRI) on a 3T Trio scanner. Structural MRI was acquired and analyzed using FreeSurfer to obtain regional brain volumes.
Results: MJ-using adolescents reported higher scores on total SSB as well as on the inhibition (DIS), experience seeking (ES) and boredom susceptibility (BS) subscales of the SSS (all $p<0.05$). Analyses of caudate volumes demonstrated that MJ users had increased total caudate volumes ($p=0.051$) which was inversely correlated with the BS subscale ($R = -0.43$, $p<0.05$). Caudate volume and BS subscales were not significantly correlated in the HC group.
Conclusions: MJ-using adolescents exhibited greater SSB, increased caudate volume and an association between total caudate volume and BS. Studies have shown that high SSB and regions involved in the dopaminergic reward pathway including the caudate are associated with addictive behavior. Our results suggest that alterations in caudate volume might be critical to understanding SSB in MJ-using adolescents.
Supported By: 1R01 DA020269-01
Keywords: Marijuana, Adolescence, Imaging

S265. Endocannabinoid Metabolism and Alcohol Consumption in Youth: A PET Study With the Fatty Acid Amide Hydrolase Radioligand [11C]CURB

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Background: Fatty acid amide hydrolase (FAAH) regulates endocannabinoid tone through degradation of anandamide, a major endocannabinoid neurotransmitter. In humans, FAAH levels are reduced by a functional genetic polymorphism (C385A, rs324420). Preclinical and genetic studies suggest that lower FAAH levels might be associated with risk for alcohol use disorder (AUD). Here, we investigated whether low FAAH levels are associated with family history of AUD or behavioural phenotypes related to risk for AUD.
Methods: FAAH brain levels were measured with positron emission tomography using the FAAH radioligand [11C]CURB in healthy male (n=15) and female (n=16) heavy drinkers aged 19-25 (21.6 ± 2 years), with either a positive (n=14) or negative (n=17) family history of AUD. Subjects completed an intravenous alcohol infusion session to assess alcohol sensitivity. Blood samples were taken to assess FAAH C385A genotype and peripherally-circulating endocannabinoid levels.
Results: Using RM-ANCOVA with FAAH genotype as a covariate, there was no difference in FAAH brain levels between family history positive and negative subjects. Alcohol and nicotine use did not differ between groups. Lower FAAH binding was correlated with greater scores on the Alcohol Use Disorders Identification Test (AUDIT) and lower sedative effects, but not stimulant effects of alcohol during alcohol challenge (Biphasic Effects of Alcohol Scale).
Conclusions: Preliminary findings show no association between family history of AUD and reduced FAAH brain levels. Lower FAAH levels, associated with increased anandamide, are related to lower subjective response during alcohol challenge and greater AUDIT scores, suggesting that lower FAAH might potentially predict vulnerability to alcohol use problems in youth.
Supported By: Ontario Mental Health Foundation
Keywords: Endocannabinoids, Alcohol Use Disorder, Youth, Fatty Acid Amide Hydrolase, Positron Emission Tomography

S266. White Matter Integrity and Lifetime Substance Consumption

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Background: Structural brain differences have been associated with various substances of abuse; however, how these differences relate to amount consumed, co-consumed substances or severity of addiction is unknown. We examined white matter integrity (FA) in a large cohort that used a variety of substances in relation to a lifetime timeline follow back (TLFB) interview and smoking severity measure.
Methods: DTI data from 255 participants (19-59 yo, 134 male) (without regular opioid use or Axis I diagnoses other than nicotine dependence, cocaine abuse/dependence, alcohol or cannabis abuse) were obtained on a 3T MRI. Smokers completed Fagerstrom Test for Nicotine Dependence (FTND). Tract based spatial statistics analyses on FA were conducted. A regression model with lifetime consumption of each substance of interest) controlling for the other substances, age and gender looked for drug effects on FA. Permutation testing with $p<0.05$ determined significance.
Results: Widespread negative correlations were found between FA (predominantly corpus callosum and internal

capsule) and lifetime nicotine and cocaine consumption. There were no relationships with cannabis or alcohol usage. Lifetime nicotine correlated negatively to FA in frontal regions, controlling for FTND. There were extensive negative correlations with FTND, controlling for lifetime nicotine.
Conclusions: Cocaine and nicotine have direct consequences on white matter integrity. However, nicotine showed a more widespread relationship with dependence severity, a behavioral feature well beyond amount consumed. Moderate levels of alcohol and marijuana consumption showed no relationship to FA, highlighting the importance of controlling for smoking and raising the possibility that dependence severity is more consequential than lifetime drug consumption.
Supported By: NIDA Intramural Research Program
Keywords: Nicotine Dependence, Cocaine Addiction, Alcohol, Marijuana, Diffusion Tensor Imaging (DTI)

S267. Structural and Functional Neural Targets of Substance Use Treatment in Adolescents With Substance Use and Addictive Disorders: A Systematic Review and Meta-Analysis

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Background: Individual differences exist in response to substance use treatment across addictive disorders, and adult neuroimaging studies indicate that structure and function of specific neural circuits may be helpful in predicting treatment response and could represent neural treatment targets. Addictive disorders have developmental etiologies and studies suggest age-related differences in treatment response and circuit-associations. The aim of this study was to qualitatively and quantitatively summarize structural and functional neuroimaging studies that examine neural correlates of treatment response in adolescents and young adults with addictive disorders.
Methods: A systematic review and meta-analysis of peer-reviewed studies following PRISMA guidelines. Studies were selected if they included individuals ages 13-24 with a DSM/ICD addictive disorder diagnosis, used neuroimaging, administered a treatment/intervention, and reported within- or between-subject contrasts in brain structure or activity across treatment/intervention and control conditions or brain-behavior correlations with treatment-outcome variables. Quantitative meta-analyses used an anatomic likelihood estimation (ALE) approach.
Results: Out of 844 citations, 13 studies were included in the qualitative analysis. Across studies, DLPFC, OFC, IFG, mFG, ACC, posterior cingulate, insula, and VS showed significant brain-behavior associations with treatment-outcome variables, while the ACC, insula and VS showed brain activity contrast between treatment/intervention and control conditions. Heterogeneity in design and methods across fMRI studies precluded quantitative analyses.
Conclusions: Neural circuits subserving cognitive/executive control, decision making, language/self-reference, and salience and affect processing are implicated in substance use treatment response for addicted youth. Larger better-controlled studies are needed. These results are consistent with findings in the adult literature and suggest overlapping neural treatment targets across developmental stages.
Supported By: NIH/NIDA K12DA000357, AACAP Physician Scientist Program in Substance Abuse (Hammond)
Keywords: Addiction, Adolescence, Functional Neuroimaging, Prediction of Treatment Outcome, Substance-Related Disorder

S268. Convergent Evidence for Predispositonal Effects of Brain Volume on Alcohol Consumption

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Background: There is growing evidence that alcohol abuse results in reduced brain volume. However, it remains unclear which regions are impacted, and the contribution of pre-existing genetic and environmental risk factors remains to be fully elucidated.
Methods: We used 3 neuroimaging samples: Duke Neurogenetics Study (DNS; N=1,303); Human Connectome Project (HCP; N=897); Teen Alcohol Outcomes Study (TAOS; N=238). We sought first to identify replicable gray matter volume correlates of alcohol consumption across the DNS and HCP. Family-based and genomic analyses were conducted to determine whether such associations are attributable to shared genetic or environmental influence. Analyses of longitudinal data tested whether brain volume was prospectively predictive of alcohol use initiation or consumption.
Results: Whole-brain analyses (DNS) found 8 clusters where greater alcohol consumption predicted reduced volume. Two of these - right insula and right superior/middle frontal gyrus — were independently replicated (HCP). Family-based analyses (HCP) revealed that the correlation between alcohol consumption and volume is attributable to shared genetic, but not environmental, influence. Polygenic risk for alcohol consumption (DNS) predicted reduced volume. In a longitudinal adolescent sample (TAOS), reduced middle frontal gyrus volume prospectively predicted the initiation of alcohol use. Similarly, in young adults (DNS), frontal volume was prospectively associated with future alcohol consumption.
Conclusions: We identify a replicable association of alcohol consumption with reduced volume of the middle/superior frontal gyrus and insula, which is largely attributable to shared genetic risk factors and is prospectively predictive of alcohol use. This work suggests that reduced volume is marker of predisposition towards alcohol consumption.
Supported By: NSF DGE-1143954; NIA R01-AG045231; NIDA 5K02DA32573; NIAAA R01-AA016274; NIDA DA031579
Keywords: Alcohol, Brain Structure, Imaging Genetics, Longitudinal Study, Biomarkers

S269. Frontostriatal Biomarkers Predict Stimulant and Marijuana Use

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Background: Recreational stimulant use is an increasing concern in young adults, as 16% of experimenters develop stimulant use disorder. Efforts to create neural biomarkers that forecast the transition from recreational to problematic use are complicated by high rates of concurrent cannabis use. This study aimed to determine whether neural indices can predict baseline and follow-up stimulant and cannabis use in a sample of occasional stimulant users (OSU).
Methods: The study utilized follow-up data from 144 OSU three years after undergoing a baseline functional magnetic resonance imaging scan during a Risky Gains Task. Dimensional analyses evaluated whether neural activation patterns predicted cumulative amount of baseline and follow-up stimulant and cannabis use. Categorical analyses evaluated whether neural patterns differentiated OSU who became problem stimulant users (PSU) from those who desisted stimulant use (DSU) at follow-up.
Results: Dimensional analyses indicated that higher interim cannabis use was linked to lower activation in frontal, parietal, temporal and insular regions during risky decisions. No significant clusters predicted baseline cannabis uses or baseline/interim stimulant uses. Categorical results indicated that relative to DSU, PSU exhibited lower frontal, insular, and striatal activation to win/loss feedback, and displayed lower thalamic activation to risky losses than wins.
Conclusions: Findings suggest that future stimulant and cannabis use can be differentiated by neural biomarkers in critical decision-making regions of the brain. Our results also suggest that baseline neural patterns best predict future cannabis use assessed from a dimensional approach whereas future stimulant use is better predicted using a categorical perspective.
Supported By: NIDA R01-DA016663, P20-DA027834, R01-DA027797, R01-DA018307
Keywords: Amphetamine, Stimulants, Cocaine, Decision Making, BOLD fMRI

S270. Effort Sensitivity to Monetary Incentive on a Decision-Making Task is Associated With Striatal Dopamine Signaling and Contingency Management Outcome in Cocaine Users

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Background: In cocaine users, a monetary incentive improves decision-making task performance, and striatal dopamine (DA) signaling is associated with the effectiveness of contingency management therapy [CM]. The current analysis examined the relationship between incentive-motivated decision-making, and CM treatment outcome and striatal DA release.
Methods: Eighteen briefly-abstinent (1-2 weeks) cocaine users (15 male) from a previous study had received the Iowa Gambling task (IGT) under both hypothetical and cash earning conditions, in addition to Positron Emission Tomography (PET) scans with [11C]raclopride with methylphenidate (60 mg) challenge and 12 week of CM.
Results: Overall, the monetary incentives appeared to influence task and clinical behavior (i.e., increased IGT effort [completion time], $p<0.05$; 83.6% cocaine-negative urine samples during CM overall). Participants (n=9) whose IGT effort was relatively more sensitive to incentive (the difference between cash and hypothetical conditions) exhibited both: 1) better CM outcomes (e.g., number of cocaine-negative urine tests) and 2) greater presynaptic DA release (ΔBPND) in the limbic striatum, relative to those participants (n=9) whose IGT effort was relatively less sensitive to incentive ($p<0.05$). No such relationship was found for other IGT indices or functional striatal subdivisions ($p>0.05$).
Conclusions: Incentive sensitivity, as indexed by changes in effort on a decision-making task, was prospectively associated with CM outcome, and may depend on DA release capacity in the limbic striatum, in cocaine users. These findings are consistent with an intermediary role for reinforcer-induced persistence, in relation to brain DA biomarkers and clinical success in incentive-based treatments for cocaine use disorder.
Supported By: NIDA
Keywords: Cocaine Addiction, PET, Contingency Management, Decision Making, Reinforcement Learning

S271. Neural Activation to Monetary Reward is Associated With Amphetamine Reward Sensitivity

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Background: One known risk factor for development of substance use disorders (SUD) is sensitivity to rewarding effects of drugs. It is not known whether this risk factor extends to sensitivity to non-drug rewards. In this study, we examined the association between neural correlates of monetary reward anticipation and sensitivity to the subjective rewarding effects of amphetamine among healthy young adults. We hypothesized that greater neural activation to anticipation of monetary reward (Win>Loss) would be associated with greater euphorigenic response to amphetamine.
Methods: Participants (N=61) completed four laboratory sessions in which they received d-amphetamine (20 mg) and placebo in alternating order, providing self-report measures of euphoria and stimulation at regular intervals. At a separate visit 1-3 weeks later, participants completed the Guessing Reward Task (GRT) during fMRI in a drug-free state.
Results: Participants reporting greater euphoria after amphetamine also exhibited greater neural activation during

monetary reward anticipation in mesolimbic reward regions, including the right caudate and putamen. A similar pattern was seen for the left caudate and putamen, but did not survive correction for multiple comparisons. Neural activation was not related to drug-induced subjective stimulation.
Conclusions: This is the first study to show a relationship between neural correlates of monetary reward and sensitivity to the subjective rewarding effects of amphetamine in humans. These findings support growing evidence that sensitivity to reward in general is a risk factor for SUD, and suggest that sensitivity of drug-induced euphoria may reflect a general sensitivity to rewards. This may form the basis of a profile of vulnerability for SUD.
Supported By: R01DA002812; K23AA025111; K01AA024519; T32MH067631
Keywords: D-amphetamine, Reward, Caudate, BOLD fMRI, Putamen

S272. Control of Impulsivity in Cocaine Use Disorder With L-DOPA: Evidence From Bold and DCM

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Background: Impulsivity is a common symptom experienced by patients with cocaine use disorder (CocUD). There are relatively few pharmacologic treatments for this problem. L-DOPA is considered as a candidate in the present study.
Methods: We conducted a pilot study on 10 CocUD subjects who completed the immediate memory task / delayed memory task (IMT/DMT) during functional magnetic resonance imaging (fMRI) session. Scans were conducted at baseline only and response to treatment was measured by monitoring number of positive drug screens on follow up as quantified by the treatment effectiveness score (TES). BOLD analyses were conducted on the pilot study group who received L-DOPA treatment ($n = 10$) using the delayed minus immediate 7 word task (DI7) contrast to assess relationship between TES and activation in various regions of interest (ROI). DCM analyses are in process and will be presented at the meeting.
Results: For the aforementioned contrast, activation in multiple frontal and motor clusters (cluster-defining threshold = 0.001; FWE-corrected 2-tailed cluster $p < 0.05$) in primarily frontoparietal, temporal, and motor areas were positively correlated with TES including one 1659 voxel cluster across the frontal, precentral, and parietal cortices. Relatively fewer negatively-correlated clusters in primarily orbitofrontal, temporal, and caudate including one 235 voxel cluster in the R orbitofrontal cortex and insula.
Conclusions: These pilot data suggest that increased activation in frontal and motor areas and decreased activation in orbitofrontal cortex predicts better response to treatment in CocUD patients treated with L-DOPA. A combination of greater and more efficient processing of responses may predict treatment response.
Supported By: NIDA Grant #U54-DA038999 (FGM/JLS)
Keywords: Cocaine Addiction, Dopamine, BOLD fMRI

S273. The Effectiveness of Injectable Extended Release Naltrexone Versus Daily Buprenorphine-Naloxone for Opioid Dependence in Short and Long Term Treatment

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Background: Extended release naltrexone is has shown promising results but has not previously been compared directly to buprenorphine, currently the most commonly prescribed treatment for opioid dependence.
Methods: A twelve-week, multi-center, outpatient, open-label randomized controlled trial followed by 9 months open follow−up study. Daily oral flexible dose buprenorphine-naloxone (4-24 mg/day) or four-weekly extended release naltrexone (380 mg). Preferred drug in the 36 week follow up period.
Results: Of 159 participants, mean age 36 years and 28% females, 80 were randomized to extended-release naltrexone and 79 to buprenorphine-naloxone. Retention in treatment was not significantly different between treatment groups with mean time 69.3 and 63.7 days, correspondingly ($p=0.325$, log-rank test). Treatment with extended-release naltrexone was non-inferior to buprenorphine-naloxone on group proportion of total number of opioid-negative UDTs (mean 0.9 and 0.8, respectively, diff. 0.1 with 95%CI:-0.04;0.2, $p<0.001$), use of heroin (mean diff. -3.2 with 95%CI:-4.9;-1.5, $p<0.001$) and other illicit opioids (mean diff. -2.7 with 95%CI:-4.6;-0.9, $p<0.001$), Superiority analysis showed significantly lower use of heroin and other illicit opioids in extended-release naltrexone group. No significant differences were found between the treatment groups on other illicit substance use. In the 9 months follow-up ($n=117$) study there was a further significant reduction in illicit opioid use from week 12 to week 48 ($p<0.01$). More adverse events were reported by extended-release naltrexone than buprenorphine-naloxone participants ($p<0.001$), most frequently occurring at treatment induction.
Conclusions: Extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining short-term abstinence from heroin and other illicit substances, and also showed high effectiveness in the follow-up study.
Supported By: Norwegian Research Council and the University of Oslo
Keywords: Long-Acting Naltrexone, Opioid Addiction, Randomized Trial, Buprenorphine

S274. Neural Circuit Mechanisms of Stress-Induced Excessive Alcohol Consumption

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Background: Alcohol use disorder (AUD) is one of the most co-occurring disorders among people seeking treatment for post-traumatic stress disorder (PTSD). It has been shown that

patients with comorbid AUD and PTSD exhibit hyper-reactivity of the amygdala upon presentations of both aversive/distressful stimuli and alcohol cues. These intriguing findings suggest that the amygdala is a key structure mediating the interactions between AUD and PTSD; however, cellular and neural circuit mechanisms underlying amygdala dysfunction in AUD and PTSD comorbidity are not well understood.
Methods: First, to establish a procedure combining a stress paradigm with a reliable behavioral measurement of associative Pavlovian learning, we employed a well-established immobilization stress (IMO) and conditioned place preference (CPP) paradigm in mice. Second, to monitor neuronal ensemble activity in a cell type-specific manner, we established optogenetic tools in partnership with high-density multi-electrode recordings.
Results: We found that IMO-stressed mice spent significantly more time in the alcohol-injected compartment of a CPP box, suggesting prior stress enhanced conditioned effects of environmental cues paired with alcohol. In parallel, light illumination and electrophysiological recordings in the amygdala were successfully performed for optogenetic-mediated cell type identification (opto-tagging) in freely moving mice.
Conclusions: Using these combined approaches, we are currently determining: 1) whether the experience of traumatic stress and subsequent alcohol consumption alters amygdala ensemble activity in a cell type-specific manner and 2) how the altered activity of molecularly distinct amygdala neurons and their projections to the nucleus accumbens (NAcc) contributes to alcohol seeking behavior after stress.
Supported By: R01 MH108665-01A1
Keywords: Alcohol Use Disorder, Post Traumatic Stress Disorder, Amygdala, Optogenetics, Electrophysiological Single Unit Recordings

S275. Failures of Oscillatory Entrainment in Individuals at Clinical High Risk for Schizophrenia

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Background: Deficits in the generation of auditory event-related potentials, including mismatch negativity (MMN) and P3 are well established in schizophrenia (SCZ). Furthermore, P3 deficits correlate with impaired entrainment of delta activity. Here, we evaluated delta entrainment during active auditory processing in clinical high risk (CHR) individuals.
Methods: Auditory ERP were obtained from 38 SCZ, 18 CHR and 34 healthy controls (HC) in an adaptive auditory oddball paradigm. Fieldtrip toolbox and BESA were used to conduct time frequency analyses of ERP data at electrode Pz.
Results: In ERP analyses, P3 amplitude was reduced in SCZ ($p=.035$) but not in CHR ($p=.8$). In time frequency analysis, SCZ showed significant reductions in 2-Hz delta activity to deviants ($p=.022$) but normal response to standards, whereas CHR showed normal deviant response but significantly increased delta to standards vs. both HC ($p=.027$ and SCZ ($p=.014$). Both SCZ ($p=.007$) and CHR ($p=.04$) showed reduced delta entrainment (ITC) relative to HC. Across groups, reduced P3 amplitude was significantly related both to reduced delta response to deviants ($p<.001$) and to standards ($p=.015$).
Conclusions: Despite reported deficits in MMN generation, no deficits in P3 generation were observed in CHR subjects. However, in time-frequency measures significant impairments in delta entrainment were observed, but were compensated by an increase in delta power. These findings suggest that during the prodromal period, CHR patients may compensate for failures in entrainment by increasing power of ongoing delta activity.
Keywords: Clinical High Risk for Psychosis, Time-Frequency EEG, P300

S276. Plasma Brain Derived Neurotrophic Factor is Negatively Associated With Interferon Gamma in Patients With Schizophrenia

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Background: Patients with schizophrenia have low levels of Brain Derived Neurotrophic Factor (BDNF) in the CNS and in the blood. BDNF promotes the survival of neurons in the brain. Plasma proinflammatory cytokines such as interferon gamma (INF-γ) have been negatively correlated with cognitive and psychotic symptoms in patients with schizophrenia. It is plausible to hypothesize that the negative impact of proinflammatory cytokines on psychotic symptoms and cognition in schizophrenia may be partly mediated by reducing BDNF levels. The aim of this study is to evaluate the association between INF-γ and BDNF in a sample of patients with schizophrenia.
Methods: 106 patients with schizophrenia [(mean age 33 (SD 12.3), 30 female and 76 male] diagnosed with the Mini International Neuropsychiatric Interview version 5, were recruited. BDNF and INF-γ were detected in fasting plasma using ELISA. Spearman's correlation coefficient was used to evaluate the association between BDNF and INF-γ.
Results: BDNF and INF-γ were negatively correlated with one another ($\rho = -0.35$, $p=0.01$).
Conclusions: The results support the notion that the negative impact of proinflammatory cytokines on brain function in schizophrenia may be partly mediated by reducing BDNF levels. Our finding could be explained by downstream effects of proinflammatory cytokines that produce oxidative stress and consequently alter the expression of trophic factors. A major limitation of this study is the absence of data on CSF/brain levels of BDNF and INF-γ. Future studies employing experimental therapeutics paradigm will shed more light on the nature of the association between BDNF and INF-γ in schizophrenia.
Keywords: Brain Derived Neurotrophic Factor, Interferon Gamma, Schizophrenia, Psychosis

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Society of Biological Psychiatry 2018 Annual Meeting

Biological Psychiatry May 1, 2018; 83:S456-S483 www.sobp.org/journal ISSN: 0006-3223

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