Biological Psychiatry
A Journal of Psychiatric Neuroscience and Therapeutics

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Aims and Scope
This international rapid-publication journal is the official journal of the Society of Biological Psychiatry. It covers a broad range of topics in psychiatric neuroscience and therapeutics. Both basic and clinical contributions are encouraged from all disciplines and research areas relevant to the pathophysiology and treatment of major neuropsychiatric disorders. Novel results of original research, in addition to Commentaries and Correspondence judged to be of high impact to the field are published, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Concise Reviews and Editorials that focus on topics of current research and interest are also published rapidly.

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Using diffusion tensor imaging, Solso et al. (Biol Psychiatry 2016, 79:676–684) examined the microstructure and volume of frontal lobe pathways in toddlers with autism spectrum disorder and found that multiple frontal pathways display axonal overconnectivity and abnormal growth trajectories. The image on the cover shows tracts with an abnormal age-related fractional anisotropy trajectory in a representative subject, including forceps minor (red), uncinate (green), inferior frontal superior frontal tract (purple), frontal projection of the superior corticostriatal tract (blue), and arcuate (brown). Tracts shown in white did not differ between typically developing and ASD toddlers. http://dx.doi.org/10.1016/j.biopsych.2015.06.029.
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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 2016); Available from http://www.icmje.org). All new manuscripts must be submitted through the journal website: http://ees.elsevier.com/bps. Please direct questions to the Editorial Office at (214) 648-0880, or Biol.Psych@utsouthwestern.edu.

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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. The main text must be no more than 4000 words, and be structured with sections entitled and ordered as follows: Introduction, Methods and Materials, Results, Discussion. Abstracts should be 250 words or less, structured with sections entitled as follows: Background, Methods, Results, Conclusions. Figures, tables, and references should be included as necessary.

Priority Communications 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 are concise (4000 words or less) and focus on current aspects of interest and research. Up to 150 references are allowed. Abstracts are unstructured and limited to 250 words. Figures and tables should summarize or illustrate important points.

Techniques and Methods articles feature new, improved, or noteworthy comments about techniques or methods relevant to basic or clinical research in, or treatment of, psychiatric disorders. Maximum length is 3000 words (main body of text only: excludes acknowledgments, disclosures, legends, and references). Abstracts are unstructured and limited to 150 words. Figures and tables should illustrate important points and are limited to ½ typeset page.

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Authors must also identify figures, tables, and/or data that have been published elsewhere. Permission from the copyright holder(s) must be obtained to reproduce or modify any previously published materials.

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Files (cover letter, text, figures) will be uploaded separately during the submission process, and should be labeled with appropriate and descriptive file names (e.g., SmithText.doc, Fig1.pdf, Table5.doc). The system will then build a single PDF of the submission from the uploaded files.

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 likely 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.

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A cover letter is required for submissions designated as Priority Communications to outline the significance of the work; it is optional for all other submissions. A cover letter must be uploaded as a separate file, as it is not made available to peer reviewers.

MANUSCRIPT

Manuscripts must be structured with sections entitled and ordered as follows: Title Page, Abstract, Text, Acknowledgments, Financial Disclosures, References, Footnotes, and Table/Figure Legends. Begin all sections on separate pages. The text of research papers should be organized into sections titled Introduction, Methods and Materials, Results, and Discussion. Tables may also be included in a text format at the end of the manuscript file. The manuscript file should be uploaded in Word, not in PDF.

Style

Manuscripts should be double-spaced. Pages must be numbered and include the first author’s name. Acronyms must be spelled out on first use in both the abstract and the text, and where used in tables or figures, in each of their legends. American spellings should be used. The location (city and state or country) of all manufacturers should be provided. Gene symbols should be italicized and differentiate by species. Human symbols should be all uppercase, whereas symbols for rodents and other species should be lowercase using only an initial capital. Protein products, regardless of species, are not italicized and use all uppercase letters. Accepted manuscripts are copyedited to conform to the AMA Manual of Style.

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On the title page, include the full names of all authors and their academic or professional affiliations, along with the corresponding author’s complete contact information. Multiple corresponding authors are not allowed. Six key words, used for indexing, should also be included. Separate list the number of words in both the abstract and article body (excluding abstract, acknowledgments, financial disclosures, legends and references), and the number of figures, tables, and supplemental information (if zero, state zero for each item). Article titles may not contain acronyms, and should be less than 100 characters. For full-length articles (Archival Reports, Priority Communications, Reviews), a short title of 55 characters or less (including spaces) must also be included. Only standard acronyms (e.g., ADHD, PTSD, etc.) and gene symbols are permitted in short titles.
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Financial Disclosures This section must include the required conflict of interest statements for each author (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 journal article (1), a book (2), and an edited book (3).


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NOMENCLATURE Psychopharmacology 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.

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GENETIC ASSOCIATION STUDIES

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RESEARCH AND DATA REPORTING GUIDELINES

Biological Psychiatry supports initiatives aimed at improving the reporting of biomedical research. Checklists have been developed for a number of study designs, including randomized controlled trials (CONSORT), systematic reviews (PRISMA), meta-analyses of observational studies (MOOSE), diagnostic accuracy studies (STARD), and animal research (ARRIVE). The Minimum Information for Biological and Biomedical Investigations (MIBBI) portal also provides data-reporting standards, such as MIAME for microarray experiments. A comprehensive list of reporting guidelines is available from the EQUATOR Network Library (http://www.equator-network.org). Authors should make use of the appropriate guidelines when drafting their papers. Peer reviewers are asked to refer to these checklists when evaluating these studies.

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Biological Psychiatry includes the consent to publication (flow diagram and checklist) at submission for all randomized controlled trials. Authors of other study designs are encouraged, but not required, to include the relevant checklists at submission. All such materials will be published as supplemental information.

Biological Psychiatry is interested in genetics/association studies that are replicable and generalizable. The following guidelines are offered in pursuit of this goal. 1) Studies need to be sufficiently large. 2) Information about subject ethnicity, and how it was determined, should be provided. The use of an analytic strategy that controls for potential stratification, such as family-controlled association, or structured association, is encouraged. 3) There must be a clear description of how the phenotype was ascertained. 4) Negative studies should always include estimates of power.

We realize that independent replication of an initial finding in the same manuscript may not be feasible in every case, but studies providing such replication of findings in an independent sample will be given highest priority. Confirmation of the functional consequences of a common disease-associated variant is useful information, but does not substitute for a rigorous demonstration of a statistically significant association. Analysis of pathways or candidate regional
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analysis is encouraged over single gene studies. Candidate gene studies must have strong positional or biological rationale or precedents in the literature that motivate gene choice.

For studies of anonymous variants, there should generally be sufficiently dense marker coverage to allow a relatively comprehensive analysis of common variants within a gene or genes. Analysis of the extent of marker coverage using standard methods to assess linkage disequilibrium should be presented. If rare sequence data should be included in the manuscript at the end of the Methods and Materials section. All microarray data (proteomic, expression arrays, chromatin arrays, etc.) must be deposited in the appropriate public database and must be accessible without restriction from the date of publication. An entry name or accession number must be included in the Methods and Materials section.

MATERIALS AND GENES Upon publication, it is expected that authors willingly distribute to qualified academic researchers any materials (such as viruses, organisms, antibodies, nucleic acids and cell lines) that were utilized in the course of the research and that are not commercially available.

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Welcome

We are pleased to welcome you to San Diego for the 2017 annual meeting of the Society of Biological Psychiatry. The theme for this year’s meeting is **Networks and Complexity in Biology, Brain and Behavior**. We are in a tremendously exciting time in Biological Psychiatry. The plenary themes will focus on the new tools available to study the brain and behavior that are unparalleled in history, and yet these remarkable developments—from optogenetic approaches in neural circuits to complex genomics to digital phenotyping—bring great challenges. How do we address the enormous amount of data, the complexity and need for integrated approaches, and the need for paradigm shifts in our thinking and methodology? Fortunately, from other areas of biology, science, and social technology, new approaches to complex analysis may bring remarkable insights to our field.

The 2017 meeting theme promises to bring an unparalleled line-up of terrific plenary speakers and symposia, addressing fascinating new approaches to complexity in neural function and activity, from mice to humans, and toward understanding language to social networks. While doing a deep dive into cutting-edge neuroscientific approaches, we will seek insights from Cancer Genomics and Multimodal Networks. Together, these efforts aim to generate exciting discussions and approaches to next-generation discovery.

We believe that the meeting themes are particularly relevant today for SOBP. Our work continues to progress into the network complexities of the brain in order to make progress toward improving the lives of our patients. By reaching out across disciplines we hope to inspire new models and thinking to resolve the complex problems of what has gone awry in bipolar disorder, schizophrenia, obsessive-compulsive disorder, and posttraumatic stress disorder and how we prevent or repair it.

With the counsel and tireless work of the Program Committee we believe that we have put together an inspiring meeting. We hope that it will be as exciting and thought-provoking for you as it has been for us to organize. If you are not already a member of the Society, please consider joining and contributing to its work. We wish you a wonderful meeting, and enjoy San Diego.

Best Wishes,

Kerry Ressler, M.D., Ph.D.
President

Paul Holtzheimer, M.D.
Chair, Scientific Program Committee
Abstracts

Society of Biological Psychiatry 2017 Annual Meeting

Thursday, May 18, 2017

PLENARY SESSION
Network Approaches to Brain Processing and Big Data
Thursday, May 18, 2017, 8:00 AM - 11:10 AM
Sapphire AN
Chair: Paul Holtzheimer

1. How Are Memories Consolidated During Sleep and Why Do We Dream?
Terrence Sejnowski
The Salk Institute for Biological Studies, La Jolla, California

Recent recordings directly from the human cortex during sleep have revealed global brain states that could be the basis for consolidating memories for facts and events. The mechanisms underlying synaptic plasticity in cortical neurons suggest that dreams may be a way to generalize from explicit memories.

References

2. Alzheimer's Prevention: Pipedream or Possibility?
Pierre Tariot
University of Arizona College of Medicine, Phoenix, Arizona

Most people know that Alzheimer's disease takes a devastating toll on patients and their loved ones. But not everyone knows that Alzheimer's prevention is no longer a pipe dream. Why is that? Laboratories around the world have illuminated many aspects of the pathobiological pathways leading to Alzheimer's, thus allowing the identification of numerous potential targets. Emerging evidence suggests that certain treatments may be more potent than others, and that very early treatment is more likely to slow the progression of Alzheimer's than waiting until the brain is ravaged. Sensitive tools are available with which to measure the disease state and impact of treatment, including during the “preclinical” stage of Alzheimer's during which silent brain changes occur. We also know that we can identify people who are at high imminent risk of symptoms. We can start prevention trials now because these pieces of the puzzle have fallen into place. The presentation will move to the Alzheimer's Prevention Initiative (API) and other prevention trials. It will highlight the unprecedented challenges inherent in this type of research, such as identifying people at elevated risk, discerning how to measure change in cognition in people without manifest symptoms, dealing with risk disclosure, obtaining funding, assuring Health Authority approvals, and attending to a host of ethical considerations. It will describe the API clinical trial in Colombia, in families plagued by the autosomal dominant PS1 E280A mutation causing early-onset Alzheimer's disease. It will describe the second API study, the Generation GeneMatch program.

References
Thursday Abstracts

3. Will Technology Transform Mental Health Care?

Thomas Insel

Verily, Pleasanton, California

Much of the work of the SOBP membership focuses on expanding our knowledge of mental disorders with a specific focus on biological mechanisms and treatments. There can be little doubt that we need a deeper understanding of the full spectrum of mental disorders. This lecture will argue for an urgent focus on bridging the gap between what we know already and what we do in practice. With a range of helpful drugs, devices, and psychosocial treatments, why have we failed to bend the curve on morbidity and mortality from mental disorders? Problems in the way we deliver care – problems in access, coordination, detection, and quality – all contribute to the egregious gap between what we know and what we do. How will we close this gap? Tools for digital phenotyping (Torous et al, 2016), online interventions (Nalsund et al, 2015), and apps for care management (www.quartethealth.com) may help to transform care by expanding access, overcoming fragmentation, facilitating detection, and improving quality. Will technology change mental health care the way it has transformed communication, commerce, and transportation? These are still early days but already we can see examples of a new system of care that promises much better outcomes with today’s treatments. To move from feasibility to effectiveness, mHealth apps will need to be tested in large-scale studies to determine if these new technologies can, in fact, reduce morbidity and mortality.

References

4. Transforming Mental Health Treatment through Innovation in Tools, Targets, and Trials

Sarah Lisanby

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Converging advances in engineering, neuroscience, and psychiatry have brought us innovations in tools, targets, and trial design which hold the potential to transform mental health care in previously unprecedented ways. An expanding array of tools are available for measuring and modulating brain structure and function, and for deeply phenotyping behavior across multiple-dimensions in real world settings. The BRAIN Initiative is accelerating the development of next generation imaging and modulation tools that promise paradigm shifting improvements in spatial and temporal precision. These high dimensionality datasets offer opportunities to link brain and behavior on the same time scale. These tools, coupled with novel computational approaches, are being leveraged to identify high yield therapeutic targets. The very definition of a target is broadening from molecular entities to include the concept of distributed circuits/systems and neural dynamics. Challenges in identifying targets remain, however, in part because our diagnostic systems are not perfectly aligned with the neurobiological basis of clinical presentations and we have gaps in knowledge of pathobiology which impede both accurate diagnosis and the ability to optimally personalize therapies. Addressing these challenges, new approaches to identifying targets seek to define tractable, objectively measurable behaviors and domains of function that are linked to targetable circuitry in a trans-diagnostic fashion. In addition to this mechanism-driven approach to target identification, studying interventions with known efficacy to discover their mechanisms of action can identify novel mechanisms and biomarkers to guide intervention development. Once targets have been identified, and tools harnessed to engage them, the experimental medicine approach to trial design is meant to ensure that the mechanism is given a rigorous test, such that either positive or negative results will be informative scientifically and importantly, can identify leads that are not worth exploring further. Finally, trial designs that examine the synergy across multiple modalities of intervention may be particularly useful as we seek to identify treatments that are effective for conditions that are refractory to monotherapies. Illustrative examples of how innovations in tools, targets, and trials offer promise to transform mental health treatment will be presented.

References
5. Mitochondrial DNA Haplogroups are Associated with Psychiatric Disease: A Nation-Wide Study of 74,763 Danes

Michael Christiansen1, Jonas Bybjerg-Grauholm1, Christian Hagen1, Vanessa Gonçalves2, Marie Bækvad-Hansen1, Christine Hansen1, Paula Hedley1, Jørgen Kanters2, Jimmy Nielsen3, Michael Theisen1, Ole Mors4, James Kennedy5, Thomas Werge6, Merete Nordentoft1, Anders Børglum2, and David Hougaard4

Background: Disturbed mitochondrial function has been implicated in psychiatric disease. Mitochondria contain a maternally inherited DNA (mtDNA) of 16.6 kb. Through evolution and genetic drift haplogroups (hgs) with a characteristic geno-geographical distribution as well as functional and pathological associations, have become fixed. We examined the association between psychiatric disease and mtDNA hgs in the Danish population.

Methods: DNA from 50,567 Danish psychiatric patients and 24,196 controls collected as part of the Neonatal Screening program from 1981 - 2005 was genotyped for 418 mtDNA SNPs on the PsychChip (Illumina). For each subject the mtDNA hg was established using signature SNPs from Phylotree. Clinical information was obtained from electronic patient files.

Results: Hg M was associated with affective disorder (n = 17260) with an OR of 0.47 (p = 2*10E-25). In a mitoGWAS, three mitoSNPs were highly associated with affective disorder (p-values: 2*10E-21), ADHD (n = 13395) with an OR of 0.50 (p = 1*10E-14), and another mitoSNP with schizophrenia (n = 2589), had a high proportion of hg A (n = 46), OR: 4.52 (p = 1.2*10E-12). In a mitoGWAS, three mitoSNPs were highly associated with affective disorder (p-values: 2*10E-25 - 2*10E-21), ADHD (p-values: 2*10E-11 – 1*10E-10), and anorexia (p-values: 6*10E-8 - 6*10E-7), and another mitoSNP with schizophrenia (p = 2*10E-11).

Conclusions: Psychiatric disease seems to be a bi-genomic disease. Haplogroup A is a risk factor for schizophrenia and haplogroup M is a protective factor for ADHD and affective disorder. However, future research is needed to define the molecular mechanism. The demonstrated association should be included in the genetic dissection of psychiatric disease.

Supported By: iPSYCH, Lundbeck Foundation, Denmark

Keywords: Schizophrenia, ADHD, Affective Disorders, Mitochondrial dysfunction, Mitochondrial haplogroup

6. Altered RNA Editing and Behavior in Prenatally Stressed Mice are Reversed by Clozapine

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1Stritch School of Medicine/Loyola University Chicago, 2University of Illinois at Chicago

Background: RNA editing that is catalyzed by ADAR enzymes is a post-transcriptional process and occurs in numerous messenger (m)RNAs that are important for neuronal function, including mRNAs that encode glutamate receptors, calcium and potassium channels. RNA editing has a profound impact on brain development and behavior. Accumulating data reveal that RNA editing plays a role in developmental disorders, mood disorders and inflammation.

Methods: Male mice exposed to prenatal stress (PRS) were tested for social interaction behavior and locomotor activity in adulthood (PND75). The effects of haloperidol and clozapine on behavior in PRS and control mice were also measured. The hippocampus was tested for altered RNA editing by QPCR of RNA editing enzymes (ADARs1-3), and targeted next-generation sequencing analysis of the RNA editing levels of 24 genes. We have also performed these tests in the hippocampus of subjects with major depression and subjects without a history of psychiatric illness.

Results: We report that mice exposed to PRS had reduced social interaction behavior and reduced hippocampal RNA editing of the AMPAR subunits GluA2-4, the potassium channel Kv1.1, and 5-HT2CR. Social interaction behavior was increased by clozapine, and this behavioral improvement was correlated with the RNA editing of GluA2 in the hippocampus but not in the frontal cortex. No other mRNAs tested had altered RNA editing in the clozapine-treated PRS mice. Analyses of human postmortem subjects are still in progress.

Conclusions: Our current data indicate that PRS is associated with many RNA editing alterations in the hippocampal epitranscriptome. Only clozapine alleviated the behavioral deficits induced by PRS. These effects of clozapine, although correlated with ADAR expression, were associated with increased hippocampal RNA editing of GluA2 but no other mRNA targets.

Supported By: Chicago Biomedical Consortium Award

Keywords: Antipsychotics, Glutamate, Next Generation Sequencing, Hippocampus, Animal Behavior

7. Altered MAP2 Phosphorylation and Dendritic Spine Density in Schizophrenia

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1University of Pittsburgh, 2University of Pittsburgh School of Medicine

Background: Lower immunoreactivity for the dendritic microtubule associated protein, MAP2, in the cerebral cortex has been reported in ~60% of individuals with schizophrenia. We recently demonstrated that in auditory cortex of subjects with schizophrenia lower MAP2: 1) was associated with dendritic spine...
reductions and 2) was not due to reduction in MAP2 protein levels. Hyperphosphorylation of the highly homologous microtubule associated protein, Tau, is known to alter its immunoreactivity and induce dendritic pathology. We therefore hypothesized that MAP2 is abnormally phosphorylated in schizophrenia, and phosphoMAP2 levels correlate with dendritic spine loss.

**Methods:** Whole gray matter was dissected from primary auditory cortex of individuals with schizophrenia and normal comparison subjects matched for age, sex, and postmortem interval, and total protein extracted. Proteins were digested with trypsin and phosphorylated peptides captured with TiO2 and analyzed by nano-flow liquid chromatography tandem mass spectrometry. Extracted ion chromatograms for all peptides were manually inspected and quantified. Temporal and parietal cortex from a cohort of monkeys chronically exposed to haloperidol, olanzapine, or sham were similarly processed and analyzed.

**Results:** Four MAP2 phosphopeptides (of 19 identified) were increased and one decreased in schizophrenia subjects (all p<0.05, Bonferroni corrected). Levels of these phosphopeptides were not altered by antipsychotic exposure in monkeys. Phosphorylations occurred at sites homologous to pathologic phosphorylations in Tau and were significantly correlated with dendritic spine reductions.

**Conclusions:** These findings demonstrate altered MAP2 phosphorylation in schizophrenia. The homology of identified phosphosites with Tau protein provide links to possible mechanisms of dendritic spine loss conserved in schizophrenia and tauopathies.

**Supported By:** MH 071533 and K01 MH 107756 from NIMH; Young Investigator Award from The Brain & Behavior Research Foundation

**Keywords:** Schizophrenia, Human Postmortem Brain, Dendritic spines, cytoskeleton, mass spectrometry

8. CRISPR/Cas9 Genome-Editing of the RERE Super-Enhancer Alters Expression of Genes in Independent Schizophrenia GWAS Regions

Cathy Barr, Yu Feng, Aidan Dineen, Karen Wigg, and Ambalika Sarkar

Krembil Research Institute

**Background:** The majority of associated markers for psychiatric disorders reside in gene regulatory regions, particularly enhancers and super-enhancers. Enhancers can reside megabases from the gene they regulate (target gene) and their targets are often not the nearest gene. Thus, the assumption that the gene nearest a GWAS-significant marker will be the risk gene will in many cases be incorrect.

**Methods:** To identify the target genes of enhancers with GWAS significant markers, we analyzed Capture-HiC data selecting enhancers for functional studies using CRISPR/Cas9 in human neural precursor cells (hNPCs). The impact on expression was measured by RT-qPCR and RNA-seq in the edited versus the mock-transfected cells.

**Results:** We selected the super-enhancer spanning the 3’ end of the RERE gene for study. Capture-HiC data indicate interactions with RERE (retinoic acid signaling co-repressor/co-activator), PARK7 (protects neurons from oxidative stress) and PER3. Using CRISPR/Cas9, we deleted a 2kb region in hNPCs. RT-qPCR showed RERE and PER3 were reduced in expression however PARK7 was upregulated. RERE, PER3 and PARK7 regulate gene expression thus we used RNA-seq to examine transcriptome changes. 107 genes were differentially expressed, including 14 regulated by retinoic acid. Importantly, 3 of these are located in independent GWAS regions for schizophrenia.

**Conclusions:** Capture-HiC provides important new leads in pinpointing the target genes of enhancer-mediated regulation emanating from the GWAS findings and functional studies confirm altered expression of interacting genes. The finding of altered expression of genes in independent GWAS regions is an important new lead in understanding the regulation of schizophrenia risk genes.

**Supported By:** Krembil Foundation, Ontario Mental Health Foundation

**Keywords:** CRISPR, transcriptome, chromosomal conformation, Schizophrenia, genome-wide association study

9. Polygenic Risk Profile Scores Should Predict Cognitive Performance in Schizophrenia but, for Individuals with a Large Premorbid/current IQ Difference, They Don’t

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1National Institutes of Health, 2CTNB, NIMH, NIH, 3Leiber Institute for Brain Development, 4Section on Integrative Neuroimaging, Clinical & Translational Neuroscience Branch, National Institute of Mental Health, Bethesda, MD

**Background:** Prior work indicates that cognitive and schizophrenia genetics overlap in affected individuals and families. We tested whether “cognitive developmental trajectory” subgroups, defined by different patterns of premorbid versus current IQ, showed different associations of schizophrenia polygenic risk profile scores (RPS) with cognitive performance.

**Methods:** Cluster analyses in 550 schizophrenia cases, using premorbid (WRAT) and current (WAIS) IQ as indicators, yielded three groups: 42% with high WRAT and IQ (SzHH), 36% with high WRAT and low IQ (SzHL), and 22% with two low scores (SzLL). Subgroup assignments were applied to 239 unaffected siblings (one per family). Schizophrenia RPS were calculated at 10 p-value thresholds using variants identified by the Psychiatric Genetics Consortium. We tested the association of RPS with general cognitive ability (“g”) by subgroup, controlling for age, sex, and population stratification.

**Results:** Cognitive performance was impaired and RPS scores were elevated in schizophrenia groups relative to controls. Siblings were intermediate. The SzHH showed significant negative associations between RPS and “g” across the more inclusive RPS thresholds (e.g., at RPS 0.05 n=173; p=.002; R2=0.051). Their siblings showed the same pattern (SibHH at RPS 0.05 n=118; p=.028; R2=0.042), as did the smaller SzLL subgroup, though non-significantly. The SzHL showed no evidence of RPS association with “g” at any threshold.

**Conclusions:** For many schizophrenia cases and unaffected siblings, RPS are inversely associated with cognition. For
the SzH-L, despite substantial polygenic risk and cognitive impairment, risk is decoupled from cognition. Different patterns of IQ performance may identify subgroups with different trajectories of cognitive development and distinct illness etiologies.

**Supported By:** NIMH Intramural Research Program

**Keywords:** Schizophrenia, Genetics, Risk profile scores, General cognitive ability, Cluster analysis

### 10. Muscarinic M1 Receptor Binding and Cognition in Medication Free Subjects with Psychosis

**Geor (I.M.) Bakker**¹, Claudia Vingerhoets¹, Matthan Caan², Oswald Bloemen¹, Jos Eersels³, Jan Booij², and Therese van Amelsvoort¹

¹Maastricht University, ²Academic Medical Center

**Background:** The underlying neurobiology of cognitive symptoms in psychotic disorders is still unclear and these symptoms are largely untreatable. Promising therapeutic effects of muscarinic M1 receptor agonists on cognitive symptoms in psychosis, suggest M1 receptor dysfunction may underlie these cognitive impairments. We therefore investigated the relation between in-vivo M1 receptor binding cognitive deficits in psychotic disorders.

**Methods:** Thirty drug-free subjects diagnosed with a psychotic disorder were assessed. M1 receptor binding potential in the dorsolateral prefrontal cortex (DLPFC), hippocampus, caudate nucleus, and putamen, regions critical for cognition and implicated in psychotic disorders was assessed using 123I-IDEX single photon emission computed tomography (SPECT). Cognition was assessed using the (CANTAB).

**Results:** Lower muscarinic M1 binding potential in the DLPFC and hippocampus was significantly related to an overall lower performance in verbal learning and memory, and lower M1 binding potential in the hippocampus to worse delayed recall for verbal memory. Lower M1 binding potentials in the DLPFC and hippocampus were also associated with more severe negative symptoms, and lower caudate and putamen M1 binding with increased presence of catatonic motor symptoms.

**Conclusions:** The current study is the first in-vivo study to relate lower muscarinic M1 receptor binding in the DLPFC and hippocampus to cognitive and negative symptoms. Additionally, a cholinergic striatal dysbalance may be implicated as part of the underlying neurobiology of catatonic motor symptoms in psychotic disorders. These results suggest that cognitive, negative as well as catatonic symptoms in psychotic disorders could benefit from M1 agonist treatment.

**Supported By:** ZonMW

**Keywords:** Muscarinic subtype 1 receptor, Psychotic Disorders, SPECT, cognition

### 11. Changes in Cellular Abundance Underlying Transcriptional Alterations in Psychiatric Patients

**Lilah Toker**, Ogan Mancarci, and Paul Pavlidis

University of British Columbia

**Background:** High-throughput expression techniques are widely used to study psychiatric disorders. A major challenge of these studies is understanding the biological impact of the identified genes. Researchers often struggle with questions such as - which cells are expressing the affected genes? Moreover, it is unclear what part of the transcriptional pattern is driven by changes in cellular abundance (e.g. due to cellular death or inflammation). Therefore, identifying the affected cell-types is crucial for the analysis and interpretation of transcriptomic data.

**Methods:** We used NeuroExpresso - a rigorously curated database of cross-laboratory brain cell-type expression data maintained in our lab, to identify marker-genres for 35 brain cell-types. We next analysed the marker-gene expression profiles in bulk-tissue data from psychiatric patients to estimate changes in the relative abundance of cells in bipolar-disorder and schizophrenia.

**Results:** We analyzed nine publicly available datasets from four different cohorts of subjects (96 control, 85 bipolar disorder, 84 schizophrenia). Strikingly, in each of the datasets we observed a significant decrease in marker-gene profiles of fast-spiking PV interneurons and an increase in marker-gene profiles of astrocytes in cortical samples from subjects with both psychiatric disorders (Wilcoxon-Mann-Whitney test, p< 0.05). No changes in astrocyte marker-gene profiles were observed in the cerebellum.

**Conclusions:** Our results suggest that the pathophysiology of bipolar-disorder and schizophrenia involves changes in marker-gene profiles of cortical astrocytes and fast-spiking PV interneurons. Cautiously, these changes can be attributed to alterations in the relative abundance of these cells, and should be accounted for when analysing and interpreting transcriptomic data.

**Supported By:** NIH (MH111099 and GM076990), NeuroDevNet

**Keywords:** Schizophrenia, Bipolar Disorder, Transcriptomics, parvalbumin interneurons, Astrocytes

### 12. Elucidating the Genetic Basis of H3-K4 Methylation in Schizophrenia and Bipolar Disorder

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¹Massachusetts General Hospital, ²Stanford University, ³Harvard University

**Background:** Dysregulated histone methylation has emerged as a recurring theme in neuropsychiatric disorders. In particular, recent GWAS of more than 65,000 subjects has suggested that accumulated common risk variants in the regulators of H3-K4 methylation may poise certain people more susceptible to major psychotic disorders, namely, schizophrenia (SCZ) and bipolar disorder (BIP).

**Methods:** We performed in-depth genomics and epigenomics data analyses of histone H3-K4 methylation pathway genes to elucidate their causal link to SCZ and BIP. First we examined whether the association of H3-K4 pathway genes are replicated in a much large GWAS dataset of the disorders available from the Psychiatric Genomics Consortium (N=35,476/48,074 cases/controls). We also investigated potential causal SNPs in the pathway genes using two brain eQTL datasets: MGH-meta-eQTL and UK-BrainEAC.
**Results:** We replicated enriched association of H3-K4 methylation pathway genes with SCZ (p = 3.1 x 10^-3) and BIP (p = 1.9 x 10^-3). Among 24 genes involved in the regulation of H3-K4 methylation (GO:51568), 10 genes showed association with both disorders at a nominal level. Interestingly, these genes were also enriched with a load of brain eQTL markers obtained from two independent datasets (p = 0.05). As a follow-up, we are currently examining the H3-K4 methylation data of 38 SCZ cases and controls obtained from the olfactory neuroepithelium tissue.

**Conclusions:** Our study confirms that genetic vulnerability of H3-K4 methylation pathway genes is a key etiologic mechanism shared between SCZ and BIP. Further studies are essential to uncover targets of dysregulated H3-K4 methylation in the two disorders and their interaction with environmental perturbations and antipsychotic treatments.

**Supported By:** NIH; NIMH

**Keywords:** genome-wide association study, schizophrenia, bipolar disorder, Histone Methylation, Epigenetics

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**ORAL SESSION**

**Clinical/Translational Neuroscience of Anxiety Disorders**

Thursday, May 18, 2017 12:30 PM - 2:30 PM
Aqua 311 AB
Chair: Isabelle Rosso

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13. Anticipatory Anterior Cingulate Cortex Activity Predicts Development of Anxiety Symptoms in Inhibited Children

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1Massachusetts General Hospital, McLean Hospital, & Harvard Medical School, 2University of Tennessee, 3Vanderbilt University

**Background:** Anxiety disorders are common, debilitating, have an early onset, and have a known risk factor; childhood inhibited temperament. However, it remains unknown why some, but not all, inhibited children go on to develop anxiety disorders later in life. Inhibited children and adults have alterations in brain activation when anticipating and viewing social stimuli. Alterations in anterior cingulate cortex (ACC) activity may predict the development of anxiety symptoms. Increased ACC activity has been associated with worry and rumination.

**Methods:** Baseline self-report and parent-report of temperament and anxiety symptoms and functional MRI data were collected on 40 children ages 8-10 years (20 inhibited, 20 uninhibited). Functional MRI data were collected during the anticipation and viewing of fear faces, neutral faces, and neutral objects. Two years later, temperament and anxiety follow-up data were collected. We hypothesized that ACC activation during the anticipation of fear faces at baseline would predict changes in anxiety symptoms within inhibited children.

**Results:** Across both groups, there was a significant decrease in self-report of anxiety symptoms over time (p < .01); however, there was no significant change in self-report of anxiety symptoms within the inhibited group. Within the inhibited group, increased ACC activation at baseline during anticipation of fear faces was associated with increases in self-report of anxiety symptoms over two years (p < .05).

**Conclusions:** Early patterns of ACC activation may be protective against the development of anxiety symptoms in high-risk, inhibited children. Teaching children to disengage the ACC during periods of anticipation or preparation may help to prevent anxiety symptoms in high-risk, inhibited children.

**Supported By:** the National Institute for General Medical Studies (T32-GM07347 to Vanderbilt Medical Scientist Training Program; JAC); the National Institute of Mental Health (T32-MHO18921); the Vanderbilt Institute for Clinical and Translational Research (UL1-TR000445-06); the Vanderbilt University Institute of Imaging Science

**Keywords:** inhibited temperament, social anxiety, Anterior Cingulate Cortex, Developmental trajectories, BOLD fMRI


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1University of Melbourne, 2FIDMAG Germanes Hospitalàries, CIBERSAM, Barcelona, 3Bellvitge Biomedical Research Institute-IDIBELL, 4University of KU Leuven, 5Hospital Universitari Parc Taulí, 6Autonomous University of Barcelona, 7Institute of Neuropsychiatry and Addictions, Hospital del Mar, Barcelona

**Background:** The study of fear extinction represents an important example of translational neuroscience in psychiatry and promises to improve the understanding and treatment of anxiety and fear-related disorders. Our objective was confirm the neural correlates of human fear extinction as assessed with fMRI via four separate meta-analyses.

**Methods:** Voxel-wise meta-analyses were conducted with Seed based d Mapping (SDM) software. fMRI studies reporting whole-brain results in association with the assessment of ‘within-session’ Pavlovian fear conditioning and extinction learning, and ‘between-session’ extinction recall were included.

**Results:** Results were included from 24 independent studies totaling over 800 participants. Meta-analyses of ‘within-session’ extinction learning, which included the analyses of early vs. late phase extinction learning, as well as extinction learning vs. initial fear conditioning, primarily confirmed the enduring nature of conditioned fear responses at a brain level, as reflected in the consistent functional activation of ‘central autonomic-interoceptive network’ regions. By comparison, ‘between-session’ extinction recall evokes a distinct neural signature involving consistent functional activation of ventromedial and dorsolateral prefrontal cortical subregions, as well as the anterior hippocampus.

**Conclusions:** Our results partially support the notion of a shared neuroanatomy between human and rodent models of fear extinction, but also suggest that an expanded account of the neurobiology of human fear extinction is possible, particularly with regard to the involvement of ventromedial and dorsolateral prefrontal cortical subregions. These findings will be discussed with the intention to inform ongoing research into fear extinction.
processes in both healthy and clinical populations, including the study of anxiety disorders and their treatment.

Keywords: Fear Extinction, fMRI, Anxiety Disorders, ventromedial prefrontal cortex, Anterior Cingulate Cortex

15. Respiratory Sinus Arrhythmia and Ventromedial Prefrontal Function in Veterans with Posttraumatic Stress Symptoms

Daniel Grupe, Joseph Wielgosz, Jack Nitschke, and Richard Davidson
University of Wisconsin-Madison

Background: Adaptive emotional responding requires flexible regulatory control of autonomic response systems, thought to involve the ventromedial prefrontal cortex (vmPFC). Individuals with posttraumatic stress disorder (PTSD) show compromised vmPFC function and parasympathetic tone—as reflected by reduced respiratory sinus arrhythmia (RSA)—yet previous studies have not drawn a direct link between these deficits.

Methods: We conducted fMRI scanning during an unpredictable threat anticipation task in 51 male veterans with a broad range of PTSD symptoms. We calculated RSA during a separate resting scan, and conducted voxelwise regression analysis across the medial prefrontal cortex to identify associations between resting RSA and task-related anticipatory threat activation.

Results: Replicating and extending previous findings, re-experiencing symptoms of PTSD were inversely correlated with resting RSA (r = -0.37, p < 0.05). Re-experiencing symptoms were also associated with relatively undifferentiated vmPFC activation across conditions of safety and threat (p < 0.05, small-volume corrected). Directly linking these two findings, we identified a novel relationship between resting RSA and vmPFC activation: veterans with reduced RSA showed less differentiated responses across conditions of safety and threat in an anatomically overlapping aspect of the vmPFC (p < 0.05, small-volume corrected).

Conclusions: The present data tie together reduced resting RSA, undifferentiated vmPFC activation, and elevated re-experiencing symptoms in combat veterans. These findings provide a theoretically parsimonious account in which intrusive trauma symptoms are associated with reduced neural control over flexible autonomic responding. More broadly, these data underscore the importance of considering individual differences in discrete symptom clusters when investigating neurobiological mechanisms of PTSD.

Supported By: NSF Graduate Research Fellowship Program; UW-Madison Institute for Clinical & Translational Research; Dana Foundation; NICHD (P30-HD003352)

Keywords: PTSD - Posttraumatic Stress Disorder, ventromedial prefrontal cortex, Respiratory Sinus Arrhythmia, Veterans, Parasympathetic Arousal

16. Sample Size Matters: A Voxel-Based Morphometry Multi-Center Mega-Analysis of Gray Matter Volume in Social Anxiety Disorder

Janna Marie Bas-Hoogendam1, Henk van Steenbergen1, J. Nienke Pannekoek2, Jean-Paul Fouche3, Christine Lochner4, Coenraad J. Hattingh4, Henk R. Cremers5, Tomas Furmark6, Kristoffer N.T. Månsson7, Andreas Frick8, Jonas Engman8, Carl-Johan Boraxbekk8, Per Carlbring9, Gerhard Andersson7, Mats Fredriksson5, Thomas Straube10, Jutta Peterburg10, Heide Klumpp11, K. Luan Phan11, Karin Roelofs12, Dan J. Stein9, and Nic. J.A. van der Wee13

1Leiden University, 2Imperial College London, 3University of Cape Town, 4Stellenbosch University, 5University of Amsterdam, 6Uppsala University, 7Linköping University, 8Umeå University, 9Stockholm University, 10University of Münster, 11University of Illinois at Chicago, 12Radboud University, 13Leiden University Medical Center

Background: Social Anxiety Disorder (SAD) is a disabling psychiatric disorder, associated with high co-morbidity. Previous research on structural brain alterations associated with SAD has yielded inconsistent results concerning changes in gray matter (GM) in various brain regions, as well as on the relationship between GM and SAD-symptomatology. These heterogeneous findings are possibly due to limited sample sizes. Multi-site imaging offers new possibilities to investigate SAD-related GM changes in larger samples.

Methods: An international multi-center mega-analysis on the largest database of SAD brain scans to date was performed to compare GM volumes of SAD-patients (n=174) and healthy participants (n=213) using voxel-based morphometry. A hypothesis-driven region of interest (ROI) approach was used, focusing on the basal ganglia, amygdala-hippocampal complex, prefrontal cortex and parietal cortex.

Results: SAD-patients had larger GM volume in the dorsal striatum when compared to healthy participants. This increase correlated positively with the level of social anxiety symptoms. No SAD-related differences in GM volume were present in the other ROIs.

Conclusions: The results suggest a role for the dorsal striatum in SAD, but previously reported SAD-related changes in GM in the amygdala, hippocampus, precuneus, prefrontal cortex and parietal regions were not replicated. Thereby, our findings indicate that sample size matters and stress the need for meta-analyses like those performed by the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium and its working groups. Actually, the collaborative effort for this work has resulted in the start of the ENIGMA-Anxiety workgroup.

Supported By: Leiden University Research Profile ‘Health, Prevention and the Human Life Cycle; Netherlands Organization for Scientific Research (NWO); EU 7th Frame Work Marie Curie Actions International Staff Exchange Scheme grant ‘European and South African Research Network in Anxiety Disorders’ (EUSARNAD); South African Medical Research Council National Health Scholarship; German Research Society (SFB/TRR-58, project C07 and STR 987/8-1); ZonMw, grant number 10-000-1002; Swedish Research Council and the Swedish Research Council for Health, Working Life and Welfare;

Keywords: Social Anxiety Disorder, Voxel Based Morphometry
17. Emotional Processing in OCD - A Meta-Analysis of 23 Functional Neuroimaging Studies

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Background: Dysfunctional emotional processing of intrusive thoughts, images and impulses is an important aspect of obsessive-compulsive disorder (OCD). Different designs have been used to study emotional processing in OCD, including symptom provocation and cognitive paradigms using emotional stimuli. However, studies show considerable variability in findings, methodology, and patient characteristics.

Methods: 23 functional neuroimaging studies comparing OCD patients and healthy controls using fMRI or PET were analyzed using seed-based d mapping. We performed a main meta-analysis comparing patients and healthy controls, and meta-regressions of medication usage, stimulus duration, symptom severity using Y-BOCS, and comorbidity. Jackknife and publication bias analyses were also performed.

Results: OCD patients, compared with healthy controls, show increased activity in the bilateral amygdala, right putamen, orbitofrontal, middle temporal, and left inferior occipital cortex during emotional processing. Right amygdala hyperactivity was most pronounced in unmedicated patients and in studies with short stimulus durations. Symptom severity was related to increased activity in the orbitofrontal, anterior cingulate cortex and precuneus. Comorbid anxiety disorders were associated with more right amygdala and putamen activity, while comorbid mood disorders were associated with more activity in the right insula and cerebellum. Comorbidit in general predicted decreased activity in the left amygdala. Jackknife analysis showed that activity in the inferior prefrontal cortex in patients and dorsomedial prefrontal cortex in controls were possibly underestimated. There was no evidence of publication bias.

Conclusions: OCD patients show increased emotional processing related activity in limbic, frontal and temporal regions. Both methodology and patient characteristics likely influence neuroimaging findings, especially regarding the amygdala activity.

Supported By: Helse Vest Health Authority (No. 911754 and 911880)

Keywords: Obsessive Compulsive Disorder (OCD), Neuroimaging, Meta-analysis, Amygdala, Anxiety

18. In Vivo Quantification of mGluR5 Availability in Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is associated with considerable emotional, financial, and social burden (McCrone et al., 2003) and heightened risk for suicide (Ramsawh et al., 2014). Yet, relatively little is known about the pathophysiology of PTSD on a molecular level. The metabotropic glutamaterge receptor (mGluR5) is implicated in animal models of fear extinction (Fontanez-Nuin, et al., 2011) and may contribute to the pathophysiology of PTSD. This study examined the relationship between mGluR5 availability and suicidality in vivo in PTSD.

Methods: Sixteen individuals with PTSD and 16 age-, sex-, and smoking-matched healthy controls participated in an [18F]FPEB PET scan and comprehensive clinical assessment. Volume of distribution (VT: ratio of activity in tissue relative to that in blood) in grey matter regions was computed.

Results: We observed significantly greater mGluR5 availability in individuals with PTSD compared to controls in brain regions implicated in the neurobiology of PTSD [dorsolateral PFC (dlPFC; 19% higher; Cohen’s d = 0.92); ventromedial PFC (vmPFC; 18% higher; Cohen’s d = 0.88), and orbitofrontal cortex (OFC; 18% higher; Cohen’s d = 0.88). Higher mGluR5 availability was associated with greater PTSD symptom severity (p < .04) and presence of suicidal ideation on scan day (p < .05).

Conclusions: This is the first in vivo investigation implicating mGluR5 dysregulation in PTSD, which be indicative of lower glutamate levels or dysregulation in the glucocorticoid system. Importantly, higher mGluR5 availability was associated with increased PTSD symptom severity and presence of suicidal ideation. Our findings suggest a potentially crucial role for mGluR5 in the pathophysiology and suicide risk in PTSD.

Supported By: NIH T32 (Davis); NIH K01 (Esterlis); NIH R01 (Esterlis); VA National Center for PTSD

Keywords: PTSD, glutamate, PET, suicide, imaging

19. Amygdala Subnuclei Volumes Differ among PTSD, Asymptomatic Trauma-Exposed and Healthy Individuals

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Background: The clinical consequences of trauma differ across individuals: while some develop post-traumatic stress disorder (PTSD), others may not present with significant psychopathology. A growing body of evidence is pointing to the anatomical and physiological properties of the fear conditioning circuitry, and the amygdala in particular, as the substrate that explains different trauma-related clinical
trajectories. In this study we use validated atlas-based methods to assess differences in the volumes of key amygdala subnuclei across patients with PTSD, asymptomatic trauma-exposed individuals and healthy controls.

**Methods:** Data was collected from 90 individuals: 34 healthy controls, 37 asymptomatic trauma-exposed, and 19 PTSD. Diagnosis was confirmed with a structured clinical interview (SCID-IV). A 3D ME-MPRAGE sequence was used to acquire high resolution 1x1x1mm T1-weighted structural MRI scan. Amygdala subnuclei volumes were derived from automated segmentation using the FreeSurfer software package. Linear Regressions were used to assess the relationship between clinical group and subnuclei volume, controlling for total intracranial volume, age and gender.

**Results:** The volumes of the right central and right basal nuclei were found to be different across groups. Smaller volumes were found in PTSD patients than asymptomatic trauma-exposed individuals or healthy controls.

**Conclusions:** These results establish significant differences in the volume of the right basal and central nuclei of the amygdala across our three groups, pointing to structural pathophysiological mechanisms.

**Supported By:** R01-MH097964 to MRM

**Keywords:** Anxiety, PTSD - Posttraumatic Stress Disorder, Trauma Exposure, Amygdala, Structural MRI

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**20. Psychobiology of Cumulative Trauma: Hair Cortisol as a Risk Marker for Stress Exposure**

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¹University of Tennessee, ²Meharry Medical College, ³University of Michigan

**Background:** Childhood trauma is associated with stress sensitization, long-lasting alterations of the hypothalamic-pituitary-adrenal (HPA) axis, and elevated risk for revictimization in adulthood. Although HPA alterations are present in the early aftermath of trauma, it is unclear if HPA activity is associated with subsequent stress levels and whether childhood trauma has a moderating influence.

**Methods:** Prospective associations between hair cortisol concentration (HCC; a measure reflecting chronic stress exposure) and changes in self-reported stress levels from baseline to 1- and 3-month follow-ups were examined in young adult women with recent (past month) exposure to interpersonal violence (IPV; physical/sexual assault) and non-traumatized controls. Childhood trauma (CT; abuse/neglect) was assessed through a self-report: 12 women met criteria for both IPV and CT (IPV/CT); 10 had either IPV or CT (IPV/CT); 15 had no IPV or CT exposure (NTC).

**Results:** The combination of cumulative trauma and HCC predicted 1-month stress level ($\beta = -0.40, t = 2.55, p = 0.017$) over and above the influence of baseline stress and depressive symptoms; lower baseline HCC predicted increases in stress levels in the IPV/CT group ($\beta = -0.69, t = 2.50, p = 0.019$) but not in the IPV/CT ($\beta = -0.26, t = 1.73, p = 0.095$) or NTC ($\beta = 0.17, t = 1.08, p = 0.289$) groups. A similar pattern was observed for the prediction of 3-month stress levels.

**Conclusions:** These findings highlight the potential utility of HCC as a predictor of elevated stress in the immediate aftermath of IPV for women with a history of CT.

**Supported By:** G12 RR003032/MD007586, K01 MH101403, and by the Betsey R. Bush Endowed Professorship in Behavioral Health at the University of Tennessee (Uma Rao)

**Keywords:** interpersonal violence; childhood trauma; hair cortisol; stress; abuse

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**SYMPOSIUM**

**Altered Neuroplasticity Mechanisms Underlying the Risk to Develop Psychopathology: Converging Evidence from Rodent and Primate Studies**

Thursday, May 18, 2017, 12:30 PM - 2:30 PM

Sapphire AB

Chair: Andrew Fox
Co-Chair: Ned Kalin

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**21. Role of BDNF in Regulating Sensitive Periods for Fear Regulation**

Siobhan Pattwell², Conor Liston¹, Joanna Giza¹, Karl Deisseroth³, and Francis Lee¹

¹Weill Cornell Medical College, ²Fred Hutchinson Cancer Research Center, ³Stanford University

**Background:** We have recently identified a peri-adolescent “sensitive period” for fear regulation, however, the circuit and molecular basis underlying these changes are not known.

**Methods:** 1) Longitudinal in vivo imaging of spine dynamics in the prefrontal cortex using microprisms allowed for the study of synaptic plasticity across adolescence. 2) Developmentally-timed delivery of BDNF ligands into the hippocampal-PFC circuitry was utilized to assess the role of this neurotrophic factor in regulating connectivity and fear-related behaviors.

**Results:** We identified dynamic hippocampal-mPFC circuit reorganization. We quantified formation and pruning rates for spines on the dendrites of pyramidal cells in the dorsal mPFC over a 24-h period from postnatal day (P)30 to P31. We found that 1-day spine formation rates in the dorsal mPFC (mean±s. d.=13.9±1.6%) were nearly triple those observed in frontal association cortex (5.0±0.9%). Using tract tracing, we observed a surge in connectivity from ventral CA1 (vCA1) and prelimbic (PL) prefrontal cortex that peaked at P30. However, genetically altered mice with a human BDNF SNP (Val66Met; rs6265) did not display this surge in connectivity. Delivery of variant BDNF into the vCA1 of wild-type mice during peri-adolescence also replicated this diminished surge in connectivity. In addition, these same mice, injected with the variant BDNF, exhibited decreased fear extinction, a key phenotype associated with the variant BDNF allele.

**Conclusions:** We have identified discrete surges in spine formation, within the PL, as well as enhanced structural vCA1-PL connectivity during adolescence. Our studies suggest developmentally specific effects on maturation of this component of the fear circuitry that is regulated by BDNF.
22. Neurotrophin-3 Signaling in the Dorsal Amygdala Decreases Early-Life Anxious Temperament in Non-Human Primates

Andrew Fox1, Tade Souaiaia2, Patrick Roseboom3, Jonathan Oler1, Rothem Kovner1, Marissa Riedel1, Eva Fekete1, Jae Mun Kim2, Joseph Nguyen2, James Knowles4, and Ned Kalin3

1University of Wisconsin-Madison, 2University of Southern California, 3University of Wisconsin School of Medicine and Public Health

Background: Early-life dispositional anxiety is a risk factor for the later development of anxiety, depressive, and substance abuse disorders. Children with an extremely anxious temperament (AT), react to novelty with increased behavioral inhibition and increased levels of physiological arousal. Our group has extensively validated a nonhuman primate model of early-life AT, and identified the central nucleus of the amygdala (Ce) as a critical part of AT’s neural substrates.

Methods: Here, we leverage the nonhuman primate model of AT to uncover molecular substrates of AT within the Ce-containing dorsal amygdala region using RNA-seq. In 46 young rhesus monkeys (Macaca Mulatta) we combined RNA-seq of dorsal amygdala tissue with brain imaging and behavioral assessments to investigate the molecular underpinnings of AT in the primate. Using real-time MRI guided surgery and an AAV5 viral vector construct, we tested our RNA-seq derived hypothesis in 5 young rhesus monkeys.

Results: RNA-seq identified many AT-related molecules, including both well-established and novel candidates. Interestingly, dorsal amygdala RNA-seq data demonstrated an inverse association between expression levels of specific neurotrophin receptor kinase 3 (NTRK3) exons and AT (t = −2.76, p = 0.009). To test the involvement of the NTRK3 pathway, we used a viral vector to overexpress the ligand for the NTRK3 receptor, Neurotrophin-3 (NTF3), in the dorsal amygdala region. Results demonstrated the dorsal amygdala NTF3 overexpression to decrease early-life AT (Mann-Whitney = 4.0, p = 0.047).

Conclusions: Together, these data provide compelling evidence that the NTF3/NTRK3 pathway is capable of decreasing anxiety in young primates, and take an important step toward understanding the molecular underpinnings of early-life AT.

Supported By: R01 NS052819, NARSAD
Keywords: Adolescence, Fear Extinction, BDNF Val66Met

24. Understanding Tetrapartite Synapses to Understand Relapse to Drug Use

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Medical University of South Carolina

Background: Altered synaptic plasticity in corticostriatal synapses has long been known to be consequential in drug addiction. However, to understand how drugs alter synaptic plasticity it is necessary to consider not just the classic presynapse from the cortex and postsynapse in the striatum, but to also consider the synaptic physiology of the astroglia surrounding the synapse and the extracellular matrix (ECM) surrounding all elements of the neuropil.

Methods: Rodents were trained to self-administer cocaine, heroin or nicotine, and tone/light cues were paired with drug delivery. After discontinuing drug, the cues were restored to reinstate behavior. Synaptic plasticity was monitored during...
the reinstatement event by measuring the strength of glutamate (AMPA) transmission, the size of the dendritic spines, and the induction of matrix metalloproteases that catalytically activate the extracellular matrix.

**Results:** We found that a prerequisite to cued-reinstatement is the enduring morphological retraction of astroglia from the synapse and/or down-regulated glutamate transport in the nucleus accumbens. This allows glutamate spillover that acts via mGluRs to promote the synthesis of nitric oxide that activates MMPs, thereby creating ligands for postsynaptic integrins. B3 integrin signaling produces a transient synaptic potentiation that parallels the time course of the reinstated behavior.

**Conclusions:** A drug-associated cue motivates the desire to seek drug through enduring changes in the relationship between astroglia and cortico-accumbens synapses. This creates vulnerability that causes drug-, but not sucrose-associated cues to activate nitric oxide and produce marked postsynaptic potentiation, which is parallel and necessary for drug-seeking. This sequence of events involves all components of the tetrapartite synapse.

**Supported By:** National Institute of Drug Abuse

**Keywords:** drug addiction, synaptic plasticity, relapse, accumbens, prefrontal cortex

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**SYMPOSIUM**

**Targeting Circuitry with Neurostimulation to Understand and Alleviate Psychiatric Disease: Beyond One Size Fits All**

Thursday, May 18, 2017, 12:30 PM – 2:30 PM
Sapphire EF
Chair: Amit Etkin

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**25. Probing Brain Networks with Transcranial Magnetic Stimulation and EEG**

Mouhsin Shafi
Beth Israel Deaconess Med. Ctr. & Harvard Medical School

**Background:** Normal brain function involves flexible interactions between distributed brain regions that together produce behavior and cognition, and disruptions in brain circuitry are believed to underlie a broad array of psychiatric disorders. Noninvasive brain stimulation with methods such as Transcranial Magnetic Stimulation (TMS), particularly when combined with other neuroimaging modalities, can be used to measure and modify brain circuit activity, and thus hold significant promise in the diagnosis and treatment of neuropsychiatric diseases.

**Methods:** TMS noninvasively produces changes in the activity of a targeted brain region. When combined with simultaneous EEG (TMS-EEG) or fMRI recordings, TMS provides a means to causally assess the cerebral response to perturbation, and produce directed changes in brain networks. We review the basic mechanisms of TMS, and describe how it can be combined with EEG to obtain information about brain network dynamics in clinical populations.

**Results:** TMS-EEG involves a number of methodological challenges that need to be carefully considered in experimental design. Careful data-processing steps are required to remove artifacts, in particular those induced by TMS. TMS produces a well-characterized EEG response that is reproducible and reliable. TMS-EEG can causally assess brain reactivity, conductivity and plasticity, and assess the balance of excitation and inhibition in human subjects. Changes in these measures have been identified across a wide variety of disease states.

**Conclusions:** TMS-EEG is a powerful tool to characterize and quantify changes in fundamental cerebral properties in psychiatric diseases, and may have significant potential in guiding treatment of abnormal brain circuits.

**Supported By:** Citizens United for Research in Epilepsy (CURE)

**Keywords:** Transcranial Magnetic Stimulation, EEG, TMS-EEG, Brain networks, Connectivity

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**26. Magnetic Seizure Therapy Changes Plasticity and Inhibition in Treatment Resistant Depression**

Zafiris Daskalakis1, Yiming Sun1, Jonathan Downar2, Paul Fitzgerald3, Tarek Rajji1, and Daniel Blumberger1

1Centre for Addiction and Mental Health, 2Toronto Western Hospital, 3Monash Alfred Psychiatric Research Centre

**Background:** Magnetic seizure therapy (MST) is a novel therapeutic option for treatment-resistant depression (TRD). Our objectives were to identify the biological indicators of suicidal ideation remission following a course of MST using combined TMS-EEG.

**Methods:** 23 patients with TRD were recruited as part of an open-label clinical trial of MST treatment. TMS-EEG measures of plasticity and inhibition were recorded from the left DLPFC within the week before MST and after an acute course of MST i.e., three times per week for up to 8 weeks. HRSD-24 and the SSI were used to assess depressive and suicidal symptoms, respectively.

**Results:** After MST, HRSD-24 and SSI scores were significantly decreased by MST treatment (p < 0.0005). Of the 18 patients with suicidal ideation at baseline, 8 patients (44.4%) had SSI remission from MST treatment. MST induced an increase in neural plasticity from frontal central electrodes (cluster p = 0.040). There was also a correlation between the decrease in LICI and the decrease in SSI over the right frontal and central electrodes (cluster p = 0.044, max at CZ, spearman rho = 0.73). LICI change in CZ correctly identified SI remitters from non-remitters with 90% sensitivity and 88% specificity (AUC = 0.9, p = 0.004). These findings were not found with TMS-EEG to the motor cortex stimulation.

**Conclusions:** Our results suggest that MST increases neural plasticity in the DLPFC. MST also decreased cortical inhibition that predicted SI remission. These findings suggest that plasticity and inhibition are key neurophysiological indicators of TRD treatment response to MST.

**Supported By:** CIHR, NARSAD, OMHF

**Keywords:** TMS-EEG, Cortical Inhibition, Neuroplasticity, TRD, Magnetic Seizure Therapy
27. Repetitive Brain Stimulation Induces Long-Term Plasticity across Patient Populations and Spatial Scales

Corey Keller1, Wei Wu1, Rachael Wright1, Lewis Kerwin1, Kasra Sarhadi1, Naho Ichikawa2, Julia Huerner3, Melinda Wong1, Andrew Yee1, Lisa McTeague4, Maria Fini5, Victor Du5, Christopher Honey6, Fred Lado7, Ashesh Mehta5, and Amit Etkin1

1Stanford University, 2Hiroshima University, 3Medical University of Vienna, 4Medical University of South Carolina, 5North Shore LJI-Hofstra Medical Center, 6Johns Hopkins, 7Montefiore Medical Center

Background: Transcranial magnetic stimulation (TMS) targeting the left dorsolateral prefrontal cortex (dPFC) is a commonly-used treatment for depression. However, our understanding of the mechanism by which TMS exerts its antidepressant effect is limited.

Methods: We randomized 30 depressed patients to daily real versus sham left dPFC rTMS (2:1 real/sham ratio), analyzed in an intent-to-treat manner with linear mixed modeling. Single pulse TMS-induced evoked potentials (TEPs) were recorded before and after treatment. Additionally, 10 healthy controls underwent a paired-pulse TEP protocol. Finally, to complement these non-invasive studies, focal repetitive electrical stimulation was applied in a rTMS-like pattern in four patients with intractable epilepsy and after-effects were quantified.

Results: We found that real rTMS was associated with a significantly greater reduction in the p60 (p<0.05) and p200 (p=0.002) potentials compared to sham rTMS, which localized to the left dPFC and medial PFC. Clinical outcomes were better for those patients with larger p60/p200 TEPs at baseline (p=0.001) or in whom there was a greater rTMS-related reduction in these TEPs (p<0.017). The paired-pulse experiment furthermore demonstrated that the p200 potential reflects intracortical inhibition. Intracranial studies also demonstrated plasticity in electrically-evoked responses after repetitive stimulation.

Conclusions: Daily rTMS induces long-lasting neuromodulatory effects temporally and spatially removed from the site of rTMS stimulation, which are highly predictive of clinical outcome, and which appear to decrease in intracortical inhibition (hence resulting in a net increase in excitability). Future applications include utilization of this TMS/EEG biomarker to optimize stimulation site, monitor efficacy, and predict treatment outcome.

Supported By: DANA foundation

Keywords: TMS-EEG, Major Depression, predictive biomarkers

28. Predictors and Correlates of rTMS Response on Resting-State Functional MRI

Jonathan Downar

University of Toronto

Background: Convergent evidence from structural and functional neuroimaging suggests that rTMS may act by targeting specific networks and ‘anti-networks’ of brain regions with correlated/anticorrelated activity, and by modulating the target region’s cortico-striatal-thalamo-cortical connectivity. Here we present new results using resting-state functional MRI to identify neural predictors and correlates of rTMS treatment outcome in major depression.

Methods: In three studies enrolling a total N=400 patients with medication-resistant depression, we obtained resting-state functional MRIs 1 week before/after 20-30 sessions of rTMS. Study 1 applied 10Hz or intermittent theta-burst rTMS to left DLPFC; study 2 applied 20 Hz, 1 Hz, or sham rTMS to bilateral DMPFC; study 3 applied 2 sessions of intermittent theta-burst rTMS to bilateral DMPFC at 60, 30, or 0 min intervals. Clinical outcomes were measured using HAMD17 and IDS30 scales. ROI-based functional connectivity analyses identified whole-brain connectivity patterns that predicted or correlated with clinical improvement.

Results: For both DLPFC- and DMPFC-rTMS, baseline cortico-cortical connectivity within two resting-state networks (salience network and ventromedial/ reward network) predicted treatment outcome. Clinical improvement was correlated with increases in corticostriatal connectivity through a dorsal-striatal node of the salience network, and with decreases in corticostriatal connectivity from ventromedial prefrontal cortex to ventral striatum. rTMS effects were markedly heterogeneous across individuals, for all protocols.

Conclusions: Therapeutic effects of rTMS may ensue via enhancement of salience-network and inhibition of reward-network connectivity on fMRI. Modulation of corticostriatal connectivity through the target region may be an important therapeutic mechanism. However, a lack of consistent neural effects across individuals may hamper many common rTMS protocols.

Supported By: Canadian Institutes of Health Research; Brain Canada; Ontario Brain Institute; Krembil Family Foundation; Edgestone Foundation.

Keywords: rTMS, Resting state fMRI, Rewards network, salience network, Major Depression

SYMPOSIUM

Translational Search for Cognitive Dimensions Underlying Schizophrenia and ASD in Humans and Mice

Thursday, May 18, 2017, 12:30 PM – 2:30 PM
Sapphire IJ
Chair: Noboru Hiroi

29. Cognition and Psychosis in Neurodevelopmental Disorders

Raquel Gur, Monica Calkins, Sunny Tang, Tyler Moore, and Ruben Gur

University of Pennsylvania

Background: Cognition has been examined in youth with subthreshold psychotic features at risk for psychosis spectrum disorders. Most studies were conducted in...
idiopathic risk populations. A growing literature focuses on 22q11.2 Deletion Syndrome (22q11DS), a neurogenetic syndrome associated with 25% risk for psychosis in youth. Prospective harmonized studies in idiopathic and neurogenetic groups can elucidate mechanisms underlying emergence of psychosis.

Methods: We examined subthreshold psychotic features, psychopathology and cognition in three large samples: Non-deleted psychosis spectrum (ND-PS) and typically developing (TD) from the Philadelphia Neurodevelopmental Cohort, and molecularly confirmed 22q11DS. Participants were assessed for subthreshold psychotic symptoms with the Structured Interview for Prodromal Symptoms (SIPS) and for psychopathology with a computerized K-SADS. The Penn Computerized Neurocognitive Battery (CNB) provided performance measures on the following domains: Executive, Episodic Memory, Complex Cognition, Social Cognition, Sensorimotor. A subsample was followed over 2-4 years.

Results: Comorbidity among psychiatric conditions was common in ND-PS and 22q11DS as it unfolds developmentally. The pattern of subthreshold psychotic features was similar. Cognition was more impaired in 22q11DS with greater developmental delay. Social and complex cognition were selectively impaired in both groups. Persistence and worsening of psychosis symptoms related to higher negative symptoms at intake and poorer functioning.

Conclusions: Features of psychosis risk are similar in idiopathic and neurogenetic samples with increased risk for schizophrenia spectrum disorders. While cognitive deficits are more pronounced in the neurogenetic sample, the similar pattern of cognitive deficits and evolution of positive and negative symptoms supports the notion of an identifiable mechanistic pathway to psychosis.

Supported By: NIMH
Keywords: Early psychosis, Neurocognition, Neurogenetics, 22q11 Deletion Syndrome, Neurodevelopment

30. Characterization of Idiopathic Autism and 22q11.2 Syndromic Forms of Autism

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Background: While 22q11.2 Deletion Syndrome (22q11.2DS) is associated with autism, less is known about autism risk in 22q11.2 Duplication Syndrome (22q11.2DupS). Moreover, it is not known which of the 30-40 genes in this region confer autism risk. We compared adaptive functioning, psychiatric symptoms and autism rates in individuals with 22q11.2DupS, 22q11.2DS, idiopathic autism, typically developing controls (TDCs), and in those with atypical 22q11.2 CNVs.

Methods: Participants matched on age and sex included 22q11.2DupS (n=28), 22q11.2DS (n=62), ASD (n=70), and TDCs (n=73). In addition, 36 individuals with atypical duplications (n=9) or deletions (n=27) of the 22q11.2 region were included. Early social communication skills, psychiatric symptoms, and cognitive and adaptive functioning at 6, 12 and 24 months were evaluated in a separate group of 210 infants at risk for autism.

Results: Individuals with 22q11.2DupS had elevated rates of autism (25%). Both the 22q11.2DupS and 22q11.2DS groups showed greater impairment than the TDC group on all social and adaptive functioning indices. A significantly higher rate of ASD diagnoses (38.4%) was observed for individuals with the proximal 22q11.2 DupS and DS than the distal 22q11.2 cases (8.7%). Atypical motor development is evident in autism at 6 months of age and by 12 months there is significant decline in adaptive and cognitive functioning and increased ASD features.

Conclusions: 22q11.2DupS and DS show increased ASD risk and impairments in adaptive and social functions. The proximal 22q11.2 region, harboring COMT and RANBP1, confers higher risk for ASD than distal regions. Study of idiopathic ASD shows impairments starting at age 6 months.

Supported By: Simons Foundation
Keywords: Autism Spectrum Disorder, 22q11.2 CNV, Human, development, atypical CNV

31. Deciphering the Molecular Mechanisms Underlying the 16p11.2 Syndromes using Rodent Models

Sandra Martin Lorenzo, Thomas Arbogast, and Yann Herault

IGBMC, CNRS, INSERM, Université de Strasbourg

Background: A large number of copy number variations (CNVs) have been associated with genomic disorders. The 16p11.2 deletion and duplication syndromes are part of those CNV syndromes with rearrangement affecting a 600Kb conserved region with 29 genes and a population prevalence of each approximately 1/2000. Symptoms indicate that 16p11.2 deletion and duplication have opposite effects on morphology, metabolism and brain function with the deletion associated with autism spectrum disorder (ASD) and the duplication with ASD and schizophrenia.

Methods: To identify dosage-sensitive gene(s) whose expression changes lead to the antagonistic phenotypes, we generated new mouse models for the deletion and duplication of the 16p11.2 homologous region and characterized the mouse models using an exhaustive series of behavioral and metabolic tests. We additionally explored the contribution of two different genetic contexts, additional parameters and single candidate genes to phenotypes.

Results: Overall, alterations of genetic dosage of the 16p11 region recapitulated human behavioral phenotypes in activity and memory in mice, but the metabolic defects were opposite in the two species.

Conclusions: The dosage imbalance at the 16p11.2 locus interacts with modifiers outside the CNV to determine the penetrance, expressivity and direction of effects in both humans and mice. We are currently using new rodent models of candidate genes to identify the major genetic driver for the 16p11.2 CNV syndromes.
32. Copy Number Variation of 22q11.2 Genes Arrests the Developmental Maturation of Working Memory Capacity and Adult Hippocampal Neurogenesis

Noboru Hiro1, Shuken Boku2, Seiji Abe3, Takeshi Izumi4, Tomohisa Takahashi5, Akira Nishi6, Hiroko Nomaru7, Yasuhiro Naka7, Gina Kang1, Akitoyo Hishimoto2, Kenji Tanigaki8, Jinghang Zhang1, Kenny Ye1, Shigeaki Kato9, Pekka Männistö10, and Kazuto Kobayashi9

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Background: Working memory capacity, a critical component of executive function, developmentally expands from childhood to adulthood. Anomalies in this developmental process are seen in individuals with schizophrenia, autism spectrum disorder (ASD) and intellectual disability (ID), implicating this atypical process in the trajectory of developmental neuropsychiatric disorders. However, the cellular and neuronal substrates of this process are not understood. We used 22q11.2 copy number variation to delve into the cellular substrates for the developmental atypicality of working memory.

Methods: We examined the effects of dose alterations of the two 22q11.2 genes, catechol-O-methyl-transferase (COMT) and Tbx1, in adult neural stem/progenitor cells of the hippocampus on working memory. Moreover, we evaluated the effect of dose alterations of these two genes on adult neurogenesis in the hippocampus in vivo and in a culture of adult neural stem/progenitor cells in vitro.

Results: Copy number elevations of COMT or Tbx1 in adult neural stem/progenitor cells in the hippocampus prevented the developmental maturation of working memory capacity in mice. Moreover, copy number elevations of COMT or Tbx1 reduced the proliferation of adult neural stem/progenitor cells and migration of their progenies in the hippocampal granular layer; no detectable effect was found for the rate of apoptosis. Knockdown of Tbx1 in vitro and constitutive deletion of Tbx1 in vivo resulted in less adult neural stem/progenitor cells in the hippocampus.

Conclusions: Our data provide evidence for the novel hypothesis that copy number variation of these 22q11.2 genes alters the developmental trajectory of working memory capacity via suboptimal adult neurogenesis in the hippocampus.

Supported By: European Union (FP7 Gencodys, grant 241995) to Y.H.; Grants from the “Agence Nationale de la Recherche” (ANR-10-CNES-02; ANR-10-LABX-0030-INRT) and the National Infrastructure for Biology and health PHENOMIN (ANR-10-INBS-07)

Keywords: Autism Spectrum Disorder, Schizophrenia, genetic dosage
34. Abdominal Adiposity is Associated with Higher Levels of Depression Severity, Cognitive Impairment and Markers of Inflammation and Insulin Resistance

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University of Texas Southwestern Medical Center

Background: While inflammatory and metabolic effects of obesity are well characterized and depend on body fat distribution, studies of depression have been restricted mostly to body mass index (BMI). This study investigated the effects of abdominal adiposity, independent of BMI, on depression in 2013-2014 National Health and Nutrition Examination Survey (NHANES) and second wave of Dallas Heart Study (DHS2).

Methods: Subjects with depression (Patient Health Questionnaire (PHQ-9) in NHANES and Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR) in DHS2) and adiposity assessments were included. Sagittal abdominal diameter (SAD, in cm) and waist to hip ratio (WHR) measured abdominal adiposity, and moderate or severe depression was defined as score ≥10 on PHQ-9 and >10 on QIDS-SR in NHANES and DHS2 respectively. Both NHANES and DHS2 measured homeostasis model assessment of insulin resistance (HOMA-IR) whereas Montreal Cognitive Assessment (MoCA) and C-reactive protein (CRP) levels were measured only in DHS2.

Results: 454 out of 5034 and 306 out of 2760 subjects reported moderate or severe depression in NHANES and DHS2 respectively. The likelihood of moderate or severe depression increased with increase in SAD (OR=1.13, 95%CI=1.06,1.19) and WHR (median-split OR=1.56, 95%CI=1.17,2.07) after adjusting for BMI and select variables. With increase in abdominal adiposity, HOMA-IR (r=0.37 in DHS2 and r=0.65 in DHS2) and CRP (r=0.16 in DHS2) increased while MoCA scores decreased (r=0.20 in DHS2).

Conclusions: Abdominal adiposity increases risk of depression, and is associated with greater cognitive impairment, systemic inflammation, and insulin resistance in depressed patients. Studies of inflammation in depression should account for body fat distribution.

Supported By: Hersh Foundation, Reynolds Foundation
Keywords: Depression, Obesity, Inflammation, insulin resistance, Cognitive Impairment

35. The Effect of Dietary Omega-6 Fatty Acids on Inflammatory Profiles Differ in Bipolar Subjects with Potential Mediation by the Microbiomic Complement

Simon Evans, Ya-Wen Chang, Charles Burant, and Melvin McInnis

University of Michigan

Background: The gut microbiome is emerging as an influential factor in mood disorders and inflammatory systems may be one mediator of the effect.

Methods: We surveyed the gut microbiome, using the stool microbiome as a proxy, from 115 individuals with bipolar disorder and 64 controls using 16S ribosomal sequencing to determine taxonomical profiles. In a separate experiment we analyzed dietary intakes and plasma cytokine profiles in 91 individuals with bipolar disorder and 75 controls.

Results: The first experiment revealed community level difference between bipolar and control subjects (Analysis of Molecular Variance, AMOVA p = 0.047), with a significantly lower fractional representation of Firmicutes faecalibacterium (p < 0.001) in bipolar, compared to controls. Faecalibacterium is a major butyrate producer and previously associated with lower inflammatory profiles. The second experiment revealed a significant negative interaction between bipolar diagnosis and intake of the major dietary omega-6 fatty acid, linoleic acid (LA), on associations with plasma IL-18, sTNFR1 and sTNFR2. These markers were all significantly associated with LA in controls, but trended toward negative associations with LA in bipolar individuals. Finally in the subset of subjects included in both experiments (n=64) faecalibacterium fractional representation significantly associated with dietary LA intake.

Conclusions: Taken together these data suggest the dietary intake of LA differentially influences inflammatory profiles in bipolar subjects relative to controls and support the hypothesis that gut microbiome profiles might mediate these differences.

Supported By: This work is supported by the Heinz C. Prechter Bipolar Research Fund and the Richard Tam Foundation at the University of Michigan Depression Center; NIH Grant #5-K01-MH-093708-04 (Evans); and The University of Michigan Medical School Host Microbiome Initiative.
Keywords: Linoleic Acid, Gut Microbiome, Cytokines and Chemokines, Bipolar Disorder, Faecalibacterium

36. Inflammatory Biomarkers as Viable Moderators of Selecting between SSRI and Bupropion in Depressed Outpatients

Manish Jha2, Abu Minhajuddin2, Bharathi Gadad3, Tracy Greer3, Bruce Grannemann3, A John Rush4, and Madhukar Trivedi1

1The University of Texas Southwestern Medical Center, Department of Psychiatry, 2The University of Texas Southwestern Medical Center, 3The University of Texas Southwestern Medical Center, 4Duke NUS Singapore

Background: Currently, there are no valid clinical or biological markers to inform treatment selection for depressed patients. Recent evidence suggests that inflammatory biomarkers may personalize selection amongst antidepressant medications with different mechanisms of action.

Methods: Participants of Combining Medications to Enhance Depression Outcomes (CO-MED) trial who provided plasma samples and were treated with either escitalopram-plus-placebo (n=51), bupropion-plus-escitalopram (n=55), or venlafaxine-pus-mirtazapine (n=60) were included as subjects. Levels of inflammatory biomarkers (Interleukin 17 or IL-17, C-reactive protein or CRP, serum amyloid P component, and alpha-2-macroglobulin) were measured using multiplex immunoassay. Changes in depressive symptom (Quick Inventory of Depressive Symptomatology Self-Report) and
Higher pre-treatment levels of pro-inflammatory cytokine IL-17 predict better outcomes with bupropion whereas lower CRP levels predict better outcomes with escitalopram. These findings support clinical use of inflammatory biomarkers to personalize antidepressant treatment selection. 

**Supported By:** NIMH, Hersh Foundation 

**Keywords:** Depression, Antidepressant response, Biomarkers, Inflammation, C-reactive protein

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**SYMPOSIUM**  
**Childhood Irritability: Insights from Multiple Brain-Based Modalities**  
Thursday, May 18, 2017, 12:30 PM – 2:30 PM  
Sapphire 400 AB  
Chair: Ellen Leibenluft

**37. Neuronal Mechanisms of Frustration and Irritability across Diagnoses**  
Wan-Ling Tseng1, Christen Deveney2, Melissa Brotman3, Joel Stoddard4, Elizabeth Moroney5, Laura Machlin3, Laura Donahue6, Jennifer Yi6, Kenneth Towbin3, Daniel Pine1, and Ellen Leibenluft3

**Background:** Although irritability is a common presenting complaint in child psychiatry, its neural mechanisms are poorly understood. Irritability is a core feature of disruptive mood dysregulation disorder (DMDD) but is present in other disorders. Thus, it is important to do trans-diagnostic studies of the pathophysiology of irritability. We used a frustrating fMRI task to model the frustrating non-reward construct in the RDoC matrix and examined associations between brain activation and irritability across three psychiatric diagnoses and healthy subjects.

**Methods:** Participants are 197 youth (Mean age=12.9 years; 49.7% girls) from groups with varying degrees of irritability: 52 DMDD, 40 attention-deficit/hyperactivity disorder (ADHD), 44 anxiety disorder, and 61 healthy volunteers. During fMRI, participants completed an attentional task in which frustration was elicited by rigged feedback. We contrasted neural activity during trials of the attentional task that followed rigged vs. positive feedback to assess how attention was impacted by preceding frustrating vs. non-frustrating events. Irritability was measured dimensionally as the mean of parent- and child-report on the Affective Reactivity Index.

**Results:** Multivariate analyses revealed that across diagnoses, higher irritability was related to greater activation in the cingulate gyrus, superior frontal gyrus, dorsolateral prefrontal cortex, and precentral gyrus, after receiving rigged vs. positive feedback (rs=.33–.37, ps<.001). These effects are independent of co-occurring anxiety and ADHD symptoms.

**Conclusions:** In highly irritable children, frustration disrupts neural function in frontal circuits mediating attention and response selection. These data have important clinical implications in identifying brain mechanisms mediating the adverse impact of frustration on cognitive function in irritable youth.

**Supported By:** This research was supported by the Intramural Research Program of the National Institute of Mental Health (NIMH).

**Keywords:** fMRI, Irritability, children and adolescence, frustration, RDoC

**38. How Much of individual Differences in Childhood Irritability can be Explained by Macroscopic Brain Morphology?**  
Giovanni Salum1, André Zugman2, Andrea Jackowski2, Luis Rohde3, Euripides Migue3, Rodrigo Bressa3, Tian Ge4, and Mert Sabuncu4

1Federal University of Rio Grande do Sul, 2Federal University of São Paulo, 3University of São Paulo, 4Massachusetts Institute of Technology

**Background:** Irritability refers to inter-individual differences in proneness to anger. It is a trait that is dimensionally distributed in the population and may reach a pathological extent. The objective of this study is to quantify the extent to which individual differences in levels of irritability can be explained by differences in macroscopic brain morphology.

**Methods:** A total of 6-14 years of age children (n=633) participated in the study. Irritability was defined using a previously validated measure from the Child Behavior Checklist (CBCL) that assessed temper tantrums and hot temper. T1 weighted images were used to estimate volumetric and thickness measures using FreeSurfer software, used as input to calculate the morphometricity measure. Morphometricity is grounded in linear mixed effects (LME) modeling, similar to what is used in population genetics to quantify SNP-based heritability.

**Results:** Irritability was not found to be significantly morphometric in our sample, with only 0.0001% (SE=14%) of the trait variability in irritability being explained by morphological differences in the brain. No other psychiatric trait as measured by the CBCL had significant morphometricity estimates; contrasting with cognitive traits such as intelligence which showed significant morphometricity estimates above 50%.
Conclusions: Brain morphology estimated from T1 weighted volume and thickness measures were not able to significantly explain variation in trait irritability. This study poses questions on whether volumetric and thickness differences among subjects can help in explaining the pathophysiology of irritability in children. It also reinforces the importance of other imaging modalities as a way to advance the understanding of the pathophysiology of irritability.

Supported By: Brazilian government institutions (FAPERGS, FAPESP, CNPq, CAPES, FIPPE)

Keywords: Irritability, Brain Imaging, Structural MRI, Developmental Psychopathology, Morphometrics

39. Temporally Sensitive Neural Measures of Inhibition in Preschool Children with Varying Irritability Symptoms

Christen Deveney1, David Pagliaccio2, Ryne Estabrook3, James Burns3, Joel Voss3, Elvira Zobel3, Melissa Brotman3, Margaret Briggs-Gowan4, and Lauren Wakschlag3

1Wellesley College, 2NIMH, 3Northwestern University, 4University of Connecticut

Background: Identifying problematic irritability in preschool children may facilitate early intervention and prevention efforts. However, the frequency of angry moods and temper outbursts among preschoolers impedes the field’s ability to distinguish between typical and atypical behaviors. Research into the brain mechanisms mediating problematic irritability in preschoolers may aid this process. Some research links irritability with abnormal medial and lateral prefrontal cortex recruitment during cognitive control tasks under non-emotional and frustrating conditions, however, studying brain functioning in young children is challenging and data are limited.

Methods: Sixty-two preschool children oversampled for disruptive behaviors completed a developmentally appropriate go/no go task under three conditions (non-frustration, frustration, and recovery). N2 and P300 event-related brain potentials to go and no go stimuli were compared across conditions. Irritability was identified from a recent bifactor model of the PAPA. Mixed linear models tested whether irritability predicts changes in N2 and P300 amplitudes across the three task conditions.

Results: Across youth, N2 and P300 amplitudes were larger during trials requiring motor inhibition (no go) versus trials without inhibition (go trials; p<.05). Greater irritability scores were associated with reduced N200 amplitudes during no go trials (β=2.0, t(276)=2.37, p=.019) and reduced P300 amplitudes during go trials (β=-2.0, t(281)=−2.73, p=.007) over the course of the task.

Conclusions: Investigations of emotional, behavioral, and neural measures of irritability in preschoolers are challenging. The present study linked higher irritability in preschoolers with reduced neural markers of inhibition over time and is consistent with prior studies linking irritability with aberrant cognitive control processes.

Supported By: NIMH R01 MH082830 (PI Lauren Wakschlag)

Keywords: Irritability, ERP

40. Neural Correlates of Adolescent Irritability and Its Comorbidity

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1University of Vermont, 2VU University Amsterdam, 3Kings College London

Background: We examined irritability (IRR) in IMAGEN, a sample of 2024 14-year-old adolescents from five European countries. Irritable mood is a very common and often impairing symptom of psychopathology and is defined by temper outbursts and proneness to anger. It has been associated with a host of psychiatric and nonpsychiatric conditions including suicide, violence, and cardiovascular disease. Relatively little is known about the neural mechanisms of irritability in childhood and adolescence.

Methods: The Development and Well-Being Assessment (DAWBA) was used to assess ADHD, MDD, ODD, and GAD. Three items from the DAWBA, selected as close matches to the Affective Reactivity Index, were used to assess irritability. Structural MRI (sMRI) was examined using whole brain Voxel Based Morphometry analysis and functional MRI (fMRI) was examined during a stop signal task of inhibitory control. sMRI and fMRI data for these regions were included in structural equation models to examine the direct and indirect associations between IRR and comorbid DSM diagnoses.

Results: A voxelwise regression analysis between GMV and irritability showed, after correcting for multiple comparisons (p<0.05), a significant negative correlation in two bilateral clusters and included the bilateral frontal gyrus and the left insula. The seven regions showing GMV reductions revealed significantly decreased activity in irritable subjects vs controls, in the bilateral superior temporal gyrus (STG), the right insula, and the right ventral pre- and postcentral gyrus (VPPG) (p<0.05), after controlling for other diagnoses.

Conclusions: Decreased GMV and less response inhibition activity was observed within the right VPPG and the bilateral STG for individuals with high IRR.

Supported By: NIGMS

Keywords: Brain Imaging, Irritability, Comorbidity, ADHD, Anxiety

SYMPOSIUM

Translational Neuroscience of Compulsive-Impulsive Disorders: Common Mechanisms in Binge Eating Disorder and Related Conditions

Thursday, May 18, 2017, 12:30 PM – 2:30 PM

Sapphire 410 AB

Chair: Eric Hollander

41. Neurocognition of Compulsive-Impulsive Disorders

Naomi Fineberg1, Claire Gillan2, Mathilde Vagh3, Annemieke Apergis-Schoute4, Samuel Chamberlain3, Paula Banca3, Eduardo Cinosi6, Barbara Sahakian5, Trevor Robbins3, and Jemma Reid3

1University of Connecticut, 2VU University Amsterdam, 3Northwestern University, 4University of Connecticut, 5Kings College London, 6University of California, San Diego
Background: Similar neurocognitive and neural abnormalities (indicating impaired cortical ‘top-down’ control) are observed across a range of compulsive-impulsive disorders. Growing evidence suggests certain brain mechanisms underpinning compulsivity are shared across diagnostic boundaries. In this lecture, we synthesise the growing evidence supporting a trans-diagnostic neurocognitive model.

Methods: We investigated a spectrum of impulsive and compulsive disorders (attention deficit hyperactivity disorder, binge eating disorder (BED), obsessive compulsive disorder (OCD), substance abuse disorders (SUD)) in a series of experiments using cognitive tasks probing aspects of behavioural inhibition, goal-directed control and habit learning, with brain-imaging.

Results: Deficits in behavioural inhibition (delay discounting, motor impulsivity, attentional flexibility) were shared across several compulsive-impulsive disorders. In OCD (N=44, versus 43 controls), impaired attentional flexibility (extradimensional set-shift) was associated with reduced rsMRI connectivity between the dorsal caudate and the lateral prefrontal cortex (P<.01). Computational modelling of decision-making in a combined patient-group with BED (N=31), SUD (N=23) and OCD (N=32) revealed a common bias from goal-directed control towards habit-learning associated with lower grey matter volumes in the caudate and medial orbitofrontal cortex (p<.05). Abnormal fMRI activation in analogous circuits was found during compulsive shock-avoidance in 37 OCD patients. Online assessment of >2000 community respondents found specific correlations between deficient goal-directed control and compulsive-impulsive disorders (ED, OCD, SUD, ICD) and with a compulsive symptom-dimension (P<.001).

Conclusions: Overlapping deficits in behavioural inhibition and in a neuro-computational mechanism favouring habit learning underlie diverse compulsive-impulsive disorders. Distributed network perturbation affects pre-frontal cortex, dorsal striatum and associated neuro-circuitry. These findings may advance development of biomarkers and treatment targets.

Supported By: Welcome Foundation (Wellcome Trust Senior Investigator Award to Prof Trevor Robbins. Ref: 104631/Z/14/Z), NIHR (UK), MRC (UK), NIDA, James S McDonald Foundation

Keywords: Compulsivity, Impulsivity, Obsessive Compulsive Disorder (OCD), Binge Eating Disorder, Neurocognition

42. Animal Models of Impulsive-Compulsive Disorders

Dawn Eagle

University of Cambridge

Background: This presentation gives an overview of some important translational animal models of cognitive neuroscience that have contributed significantly to our understanding of the neural basis of impulsive-compulsive disorders. I will describe key findings from these translational animal studies, which highlight similarities and differences in the neural circuitry and neuropharmacology underpinning impulsive and compulsive behavioural control.

Methods: The presentation describes a range of tasks that translate directly across species and cover cognitive components across the impulsive-compulsive spectrum. I will describe findings from the Stop-Signal Task, the 4/5-Choice Serial Reaction Time Task, and the Observing Response Task, a task that evaluates the development of compulsive checking.

Results: Multiple studies have shown that comparable neural mechanisms (both in terms of neural circuitry and neurotransmitter action) underpin important features of impulsive and compulsive behavioural control in rodents, non-human primates and human. The results show that good, fully-translational cognitive tests provide an effective link between previously-disparate fields within neuroscience research.

Conclusions: This presentation concludes that cognitive neuroscience models that translate directly across species are vital research tools for the integration of fundamental neuroscience and clinical study. Further development of such models in other cognitive domains should be encouraged.

Supported By: Wellcome Trust Programme grants, awarded to TW Robbins, BJ Everitt, BJ Sahakian, AC Roberts and JW Dalley

Keywords: Obsessive Compulsive Disorder (OCD), ADHD, Translational research, Animal Model

43. Overview of Data Supporting the Efficacy of Lisdexamfetamine Dimesylate in the Treatment of Binge Eating Disorder

Susan McElroy

Lindner Center of HOPE/University of Cincinnati College of Medicine

Background: The stimulant pro-drug lisdexamfetamine dimesylate (LDX) is the only drug that has regulatory approval for the treatment of binge eating disorder (BED).

Methods: In this presentation, the randomized controlled trials (RCTs) supporting this indication will be reviewed.

Results: In the first RCT of LDX in BED, a Phase 2 dose-finding and proof of concept trial, LDX at 50mg/d and 70mg/d, but not 30mg/d, was superior to placebo for reducing binge eating behavior, as well as obsessive-compulsive features of binge eating and trait impulsivity. The efficacy of LDX in BED was then evaluated in two identically-designed 12-week, multicenter, dose-optimization, double-blind, placebo-controlled trials. In both studies, LDX (50 or 70 mg/d) was again superior to placebo for reducing binge eating behavior and for reducing obsessive-compulsive features of binge eating (impulsive traits were not assessed). In a fourth study, the anti-binge eating effect of LDX was shown to persist for six months in a double-blind, placebo-controlled, randomized withdrawal study. Patients who responded to 12 weeks of open-label treatment with LDX 50 or 70 mg/day (n = 275) were randomized to receive continued LDX or switched to placebo for six months. Based on a Cox proportional hazards model, the estimated hazard for relapse with LDX was 11 times less than placebo (hazard ratio = 0.09). Specifically, 5.0% of LDX-treated patients relapsed as compared to 34.4% of placebo-treated patients.
**Conclusions:** The implications of these data for BED and for other potential impulsive-compulsive disorders will be discussed.  
**Keywords:** Binge Eating Disorder, lisdexamfetamine, obsessive compulsive

44. Experimental Therapeutics, Mechanism of Action, and Striatal Gradients in Compulsive and Impulsive Disorders

**Eric Hollander**, Stefano Pallanti, Sue McElroy, and Naomi Fineberg

1Albert Einstein College of Medicine, 2University of Florence, 3University of Cincinnati, 4University of Hertfordshire

**Background:** Experimental therapeutic trials in compulsive-impulsive disorders have evaluated impact of treatment on obsessive thoughts, compulsive behaviors, impulsivity and cognitive restraint. Little work has integrated findings from animal models and human neuropsychology along with therapeutic response in order to elucidate the link between mechanism of action and impact on striatal brain circuitry in these conditions.

**Methods:** Phase 2 and phase 3 trials in binge eating disorder (BED) (lisdexamfetamine), OCD (SSRIs) and pathological gambling (PG) have evaluated impact of treatment on obsessive thoughts, compulsive behaviors, impulsivity and cognitive restraint. Studies have also examined treatment effects of these agents on neurocognition and frontostriatal activity.

**Results:** Modest to large effects sizes have been demonstrated in compulsive and impulsive disorders on measures of compulsivity, impulsivity and restraint with stimulants (BED), SSRIs (OCD) and lithium (PG). Impact on neurocognitive measures that reflect fronto-striatal gradients is also known and can be interpreted in light of respective therapeutic mechanism of action. Factor analysis in BED has demonstrated a 3-factor solution of impulsive, obsessive and compulsive factors that correlate with ventral striatum, dorsal striatum (caudate) and putamen gradient.

**Conclusions:** The compulsive-impulsive domain is the target of drug-development efforts. The neurocognitive measures of wait (delayed discounting), stop (stop-signal), shift (ID-ED set-shifting) and habit correspond to ventral striatal gradients in animals and humans. Understanding mechanism of action in these conditions impacts on drug development efforts in these compulsive-impulsive disorders.

**Supported By:** NIMH, NIDA, NINDS

**Keywords:** impulsive, compulsive, experimental therapeutics, binge eating disorder, OCD

45. The Subthalamic Nucleus at the Nexus of Decision-Making Processes

**Christelle Baunez**

CNRS

**Background:** The Subthalamic nucleus (STN) is known for its role in the control of inhibition and especially impulsivity of action. Since STN deep brain stimulation can treat OCD, it is important to better clarify the role of STN in impulsivity of action and decision-making. These behaviors are guided by reward and the role of STN in reward-related encoding has been studied in rats, monkeys and Parkinson’s Disease (PD) patients.

**Methods:** In the rat, we have assessed the effects of STN lesions on two dissociable behaviors: 1) decision-making between smaller-certain versus larger-uncertain rewards (0, 50 or 100%) in a probabilistic discounting task (PDT) 2) choice of smaller-certain versus larger-uncertain penalties in an animal model of loss-chasing behavior. In monkeys and parkinsonian patients, we have recorded STN neurons while the subjects were performing a task in which a certain effort had to be produced to obtain a reward of various possible sizes. This allowed us to address encoding of the cost/benefit subjective value.

**Results:** STN lesions decrease responding for uncertain outcomes. In the first task, when the probability was 50% to obtain the large reward, STN rats chose the certain small reward. In the loss chasing task, STN rats quit instead of chasing losses. In monkeys and PD patients, STN neurons encode cost/benefit values at the presentation of the cues.

**Conclusions:** These results highlight the role of STN in decision-making guided by rewards that could therefore be affected in patients treated by STN DBS in various pathologies.

**Supported By:** CNRS, Fondation de France, ANR, Aix-Marseille Université

**Keywords:** basal ganglia, impulsivity, cost/benefit, reward, motivation

46. Pause-Then-Cancel: A Two-Step Account of Behavioral Inhibition via Complementary Basal Ganglia Pathways

**Joshua Berke**

University of California - San Francisco

**Background:** Humans and other animals learn to vigorously perform actions that reliably lead to rewards, and such behavior is critically dependent on the basal ganglia. Yet circumstances can change, so to maintain behavioral flexibility additional mechanisms are needed to delay and/or suppress well-learned actions. We are therefore investigating the distinct functional roles of specific basal ganglia circuits in behavioral inhibition, with the goal of understanding both normal mechanisms of decision-making and how these go awry in psychiatric disorders.

**Methods:** Single-neuron electrophysiology and optogenetics in rats performing stop-signal tasks.

**Results:** We have demonstrated that the subthalamic nucleus to substantia nigra pars reticulata pathway provides a rapid Pause signal in response to unexpected cues, while a
complementary globus pallidus to striatum projection helps cancel actions by quashing developing action representations. We are now comparing these functions to those played by the striatal indirect ("NoGo") pathway and striatal fast-spiking interneurons. We tested the hypothesis that the indirect pathway represents the evidence that specific actions do not lead to reward; surprisingly our results so far (based on n=260 neurons recorded in striatal and globus pallidus from n=9 rats) suggest that this type of information processing is performed by the fast-spiking interneuron population instead.

**Conclusions:** Multiple psychiatric conditions including ADHD, Tourette Syndrome, and compulsive drug use involve basal ganglia dysfunction and are characterized by failure to suppress maladaptive behaviors. By understanding how specific basal ganglia subcircuits contribute to action suppression we may identify superior targets for therapeutic intervention.

**Supported By:** R01 MH101697; CHDI

**Keywords:** striatum, behavioral inhibition, parvalbumin

**47. Preferential Role of the Subthalamic Nucleus in Avoidant Decision Making**

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1Harvard Medical School, Massachusetts General Hospital, 2Massachusetts General Hospital

**Background:** The subthalamic nucleus (STN) is an important node in a cortical-subcortical network that facilitates decision making under conflict and processes feedback to shape future behavior. The STN is also the most common site of deep brain stimulation (DBS) to treat Parkinson’s disease, but has been associated with a range of cognitive and psychiatric side effects including mania and impulsivity.

**Methods:** We recorded from single neurons in the human STN during implantation of DBS electrodes. Patients engaged in two novel behavioral tasks designed to assess risk tolerance (Gambling task) and approach-avoidance decision making (Aversion-Reward Conflict task). To assess the effects of STN stimulation, subjects also performed the task as outpatients while they received brief bursts of task-synchronized STN stimulation through their DBS electrodes.

**Results:** Across the two tasks, the population STN spike rate was positively correlated with low-risk and avoidant decision making, and predicted whether subjects would make high or low-risk choices when the risk-benefit ratio did not definitively favor either choice. STN spike rates were also positively correlated with the degree of decision conflict. As predicted by the population spike rate, STN burst stimulation during the pre-decision epoch biased subjects to make more conservative choices.

**Conclusions:** The STN is preferentially engaged before high-conflict and avoidant decisions and high-frequency STN stimulation biases subjects towards low-risk choices under decision conflict. The preferential engagement of the STN during avoidant decision making suggests a role for adaptive STN stimulation to mitigate neuropsychiatric symptoms.

**Supported By:** Anne Young Fellowship in Movement Disorders, the Bachmann Strauss Dystonia and Parkinson Foundation and the AAN/ABF Clinical Research Training Fellowship to TMH. DOD/DARPA W911NF-14-2-0045 to EE and DD.

**Keywords:** Subthalamic Nucleus, Deep Brain Stimulation, Avoidance, Impulsivity, Parkinson’s disease

**48. Decisional Impulsivity and the Anterior Limbic-Associative Subthalamic Nucleus in OCD: Stimulation and Functional Connectivity**

Valerie Voon1, Fabien Droux2, Laurel Morris1, Stephan Chabardes2, Thierry Bougero2, Olivier David2, Paul Krack2, and Mircea Polosan2

1University of Cambridge, 2University of Grenoble

**Background:** Rapid decision making and delay discounting are forms of decisional impulsivity. The subthalamic nucleus (STN) is implicated in inhibitory function but its role in decisional impulsivity is less well-understood. Deep brain stimulation (DBS) of the limbic-associative STN is effective for obsessive-compulsive disorder (OCD). We investigate (i) decisional impulsivity in OCD subjects who have undergone STN DBS and (ii) the relationship with STN functional connectivity in healthy controls.

**Methods:** We test OCD subjects on and off DBS in a randomized counterbalanced double blind manner on evidence accumulation during probabilistic uncertainty (Beads task) and delay discounting. We use resting state functional connectivity in healthy controls to parcellate limbic-associative and motor cortical connectivity with STN.

**Results:** STN DBS in OCD (N=12) increases decisional impulsivity with less evidence accumulation and greater delay discounting. In healthy controls (N=154) we show peak connectivity of anterior limbic-associative (ventral striatal, dorsolateral prefrontal cortex, dorsal cingulate) and posterior motor STN (supplementary motor area and M1). Plotted optimal DBS contacts converge in anterior STN in OCD patients. In healthy controls (N=54), evidence accumulation correlates with anterior associative-limbic STN and right dorsolateral prefrontal functional connectivity.

**Conclusions:** We highlight the anterior associative-limbic STN in increasing decisional impulsivity suggesting impaired action outcome mapping in the context of uncertainty. STN stimulation shifts evidence accumulation in OCD towards a functional less cautious adaptive style closer to healthy controls. We replicate in humans, tracing studies conducted in primates dissociating limbic-associative and motor hyper-direct cortical connectivity with STN subregions. Localization of STN stimulation may have clinical implications for behavioural symptoms.

**Supported By:** Wellcome Trust

**Keywords:** Deep Brain Stimulation, Impulsivity, Obsessive Compulsive Disorder (OCD), Subthalamic Nucleus, Resting state functional connectivity
Background: This talk will examine the role of maladaptive myelination as a potential mechanism underpinning individual variability of the stress response. Changes in white matter organization have been observed in depression, schizophrenia, PTSD and suicide, suggesting that altered myelination may be a novel and underappreciated mechanism by which psychopathologies emerge.

Methods: Juvenile or adult rodents were exposed to stress, and neurogenesis, oligodendrogenesis and myelination rates quantified in the hippocampus, and correlated with anxiety scores. Transcriptional programming of neural stem cells studied in hippocampal stem cell cultures and lineage tracing of stem cell progeny in a transgenic mouse model.

Results: We recently demonstrated in a rodent model that adult stress exposure redirects the developmental fate of adult neural progenitor/stem cells (NSC) in the dentate gyrus, a gray matter structure, causing cells fated to become neurons to differentiate instead into oligodendrocytes (Chetty et al, Mol Psych, 2014). Recently, subjects with PTSD secondary to adult trauma exposure were shown to have increased myelin content in the hippocampus gray matter. Moreover, symptom severity significantly predicted myelin content in these regions (Chao, et al, Front. Neuro. 2015). Similarly, in a rat model of trauma hippocampal oligodendrogenesis rate and grey matter myelin content is increased following a single severe stressor, and correlated with a composite of anxiety symptoms.

Conclusions: Our results suggest a novel model in which stress may carry long term consequences on brain function by modulating oligodendrogenesis and myelination in grey matter, thereby altering cellular composition and functional connectivity of the brain.

Supported By: NIMH BRAINS (MH087495) award and NARSAD Independent Investigator award to DK.

Keywords: stress, myelin, glia, plasticity, PTSD, development.

Tuesday Abstracts
Keywords: brain responses to trauma. Adaptive myelination is a novel mechanism for understanding compared to other mechanisms such as adult neurogenesis. plasticity potentially has a far greater reach in the adult brain brain abnormalities in PTSD. It represents a form of adaptive development is a novel mechanism underpinning the structural

Conclusions: The results suggest that maladaptive adult myelin development is a novel mechanism underpinning the structural brain abnormalities in PTSD. It represents a form of adaptive plasticity potentially has a far greater reach in the adult brain compared to other mechanisms such as adult neurogenesis. Adaptive myelination is a novel mechanism for understanding brain responses to trauma.

Supported By: Department of Defense- W81XWH-11-2-0189 Keywords: PTSD, Cortical myelin, MRI brain imaging, Memory

52. Is Chronic Severe PTSD Associated with Excess Myelin in the Amygdala?

Steven Woodward¹, Marie Schaar², Janice Kuo³, and Danny Kaloupek⁴

¹National Center for PTSD, Dissemination and Training Division, ²University of Geneva, ³Ryerson University, ⁴National Center for PTSD, Department of Veterans Affairs

Background: There is consensus that amygdala manifests functional changes in association with PTSD; however, even large studies of amygdala structure in PTSD have produced conflicting results. Morey (2012) studied 200 Veterans using FreeSurfer and found amygdala volume to be smaller in association with PTSD; while Kuo (2012) used manual delineation in 99 Veterans and found it to be larger.

Methods: We reanalyzed the Kuo (2012) data collected from 99 combat Veterans (51 PTSD+/48 PTSD−) at 1.5T with FreeSurfer to determine whether method variance could account for the differences between our results and those of Morey. Amygdala volumes were calculated automatically using FreeSurfer (v.S; Fischl et al, 2002) and compared to the manually-delineated volumes obtained using BrainImage (Reiss; Kates et al, 1997). In addition, T1-weighted intensity histograms were obtained from the FreeSurfer volumes and separate gray- and white-matter components extracted using BrainImage.

Results: Amygdala white matter volume violated the pattern of high cross-method agreement, and was significantly larger in the PTSD subsample. The gray matter component of amygdala volume was not associated with PTSD, but replicated the interaction of early childhood adversity and adult combat exposure on total amygdala reported by Kuo. Employing the Jensen-Shannon divergence measure, T1-weighted intensity histograms in amygdala were more similar to white matter in PTSD+ than in PTSD− participants.

Conclusions: These results are consistent with activity-dependent myelination (cf. Fields, 2015) and may be interpretable through the Glasser and Van Essen model of competition between myelination and synaptogenesis. A follow-up study using methods borrowed from the MS literature is now underway.

Supported By: Veterans Administration and U.S. Army Medical Research and Material Command

Keywords: PTSD - Posttraumatic Stress Disorder, Amygdala, Veterans: Co-Chair: Daniela Kaufer, University of California, Berkeley

53. Depression and Aging: A Double Hit to the Semantic Memory Network

Sara Weisenbach¹, Michelle Kassee², Julia Rao², Robert Welsh¹, Jon-Kar Zubieta¹, and Scott Langenecker²

¹University of Utah, ²University of Illinois at Chicago

Background: During older age, Major Depressive Disorder (MDD) has been associated with cognitive deficits in multiple domains. Our previous work has demonstrated an interaction of age with disease on the functioning of the cognitive control network (Rao et al., 2015). The current study was designed to now investigate the interaction of age with disease on the semantic memory network.

Methods: 69 young adults (35 MDD) and 47 older adults (24 MDD) underwent fMRI while performing the Semantic List Learning Test, a measure of verbal memory encoding. The main contrast of interest was activation during encoding of novel word lists (relative to distraction).

Results: After correcting for multiple comparisons, all groups activated regions relevant to attention and encoding, including medial temporal regions. There is a main effect of age in eight regions, including anterior cingulate and caudate body, in addition to other regions in frontal, parietal, and subcortical areas (younger>older). There is a main effect of disease (healthy>MDD) in eight regions, some of which overlap with regions showing a main effect of age (i.e., anterior cingulate, caudate body). Post-hoc analyses show that the effect of disease is primarily driven by reduced activation in the older depressed group relative to their never-depressed peers.

Conclusions: Findings demonstrate a double burden of age and disease on the functioning of the semantic memory network. Interestingly, there are disparate underlying neural activation patterns for cognitive control (increased) relative to memory (decreased). Functional neuroimaging changes might be developed as biomarkers of emerging dementia among older adults with depression.

Supported By: NARSAD, University of Michigan Depression Center, University of Michigan IMRI Laboratory, Michigan Alzheimer's Disease Research Center

Keywords: Functional MRI, Brain Aging, Major Depressive Disorder (MDD), Brain Imaging, Memory
54. Pathological Brain Aging Influences on Late-Life Depression and Antidepressant Outcomes

Warren Taylor
Vanderbilt University

**Background:** Late-life depression is characterized by mood and cognitive symptoms and an increased risk of dementia. It remains unclear how Alzheimer and vascular pathology contributes to risk of depression and whether this pathology affects treatment response. We hypothesized that medial temporal lobe alterations and deficits in cerebral blood flow (CBF) would be associated with depression and poor antidepressant responses.

**Methods:** Adults aged 60 years and older were recruited from the community. Participants completed baseline MRI, including an assessment of medial temporal lobe subfield volumes, cerebral blood flow with arterial spin labeling, and resting-state functional connectivity. Depressed participants completed twelve-weeks of open-label treatment with sertraline.

**Results:** Depressed elders did not exhibit differences in hippocampal subfields, but did exhibit smaller perirhinal cortex volumes, a key temporal region involved in memory. In contrast, we did not observe group differences in regional CBF and, in depressed subjects, we did not find a relationship between antidepressant response and reduced CBF. However, we did observe that increased CBF in the lateral orbitofrontal cortex and anterior cingulate gyrus predicted poorer response to sertraline.

**Conclusions:** Late-life depression is associated with medial temporal lobe alterations, potentially linking depression with risk of dementia. As the perirhinal cortex is a site of early amyloid deposition, we may be observing early volumetric effects of that process. In contrast, we found no evidence that perfusion deficits measured by CBF were related to depression. However, we did observe that increased frontocingulate CBF, possibly related to underlying metabolic activity, predicted poor antidepressant response.

**Supported By:** R01 MH102246; R21 MH 099218

**Keywords:** Geriatric Depression, Antidepressant response, Aging, MRI

55. Intrinsic and Internetwork Connectivity, Negativa Self Referential Processing, and Antidepressant Response in Late-Life Depression

Faith Gunning
Weill Cornell Medicine

**Background:** The cognitive control network (CCN) and default mode network (DMN) are preferentially susceptible to advancing age and have been implicated in both the cognitive and mood symptoms often observed in older adults. Negative self-referential processing is a hallmark feature of depression and may contribute to poor treatment outcomes. Negative self-referential processing during the depressed state as measured by both self report (Brooding Subscale of the Rumination Response Scale; r = −.47) and a performance-based measure (Trait Adjective Task; r = −.44). These relationships persisted following treatment with escitalopram. Lower baseline white matter integrity suggested that structural connectivity between the dorsal ACC and middle frontal gyrus nodes of the CCN predicted persistence of negative self referential processing (r = −.49) following treatment.

**Conclusions:** Structural and functional connectivity within and between the DMN and the CCN may contribute to the expression and persistence of the negative self-referential processing that is a hallmark in late-life depression.

**Supported By:** R01 MH1097735

**Keywords:** Major Depressive Disorder (MDD), Cognitive Control Network, Default Mode Network, Connectivity

56. Connectomic Correlates of ECT Treatment and Response

Olu sola Ajirole1, Reza Tadayonnejad1, Alex Leow1, and Chris Abbott2

1University of Illinois at Chicago, 2University of New Mexico, Albuquerque

**Background:** Previous work by our group and others using multimodal neuroimaging techniques have demonstrated that major depression (MDD) is associated with network-level alterations such as reduced network efficiency, altered hub organization, and decreased connectivity in reward circuitry. The goal of the present study was to determine whether electroconvulsive therapy (ECT) can correct or compensate for global and local network-level alterations observed in MDD.

**Methods:** We examined 68 participants (42 diagnosed with MDD and 26 healthy comparison (HC) subjects) who underwent resting-state functional magnetic resonance imaging (rs-fMRI) scanning. MDD participants were scanned before and after ECT. HC subjects were scanned at a similar interval. Functional connectomes were generated from the rs-fMRI data. Global and nodal graph theory based metrics were calculated. Effective connectivity within the reward network was also measured. We examined the effect of disease (MDD vs. HC), effect of ECT treatment (time 1 vs time 2), and correlations with ECT treatment response.

**Results:** Depressed subjects had significantly reduced global efficiency compared to HC, which remained significant after ECT. Baseline nodal efficiency in the frontal pole and inferior gyrus was significantly associated with treatment response. Hub strength in the hippocampus (r = −.44, p = .004) and right supracalcarine cortex (r = −.47, p = .002) were significantly associated with treatment response.
Conclusions: These results demonstrate that altered local network properties in limbic and reward circuitry can be improved with ECT and correlate with treatment response. Thus, these local brain network alterations may serve as potential neuroimaging-based biomarkers for ECT response.

Supported By: The Dana Foundation Brain and Immuno-imaging and Centers of Biomedical Research Excellence to Chris Abbott, M.D. (2P20GM103472-01).

Keywords: Neuroimaging, connectome, Electroconvulsive therapy, Major Depression

Advances in Peripheral Epigenetic Studies of Posttraumatic Stress Disorder
Thursday, May 18, 2017, 12:30 PM – 2:30 PM
Aqua EF
Chair: Alicia Smith

57. Genome-Wide DNA Methylation Comparison by Illumina Epic Array between Live Human Brain and Peripheral Tissues within Individuals

Gen Shinozaki1, Patricia Braun2, Benjamin Hing3, Yasunori Nagahama3, Lindsey Gaul2, Jonathan Heinzman2, Melissa McKane2, Andrew Grossbach3, Brian Diouhy3, Matthew Howard3, Hiroto Kawasaki3, and James Potash2

1Department of Psychiatry, University of Iowa Hospitals and Clinics, 2Department of Psychiatry, University of Iowa, 3Department of Neurosurgery, University of Iowa

Background: DNA methylation (DNAm) is a critical epigenetic mark impacting gene expression, and differential DNAm in the brain is associated with many psychiatric diseases. However, access to brain tissues to assess DNAm is essentially limited to post-mortem samples. The use of surrogate tissues, such as blood and saliva, has become common in identifying methylation changes associated with psychiatric disease. However, there is no literature showing direct association of DNAm between brain and peripheral tissues to support the validity of such surrogate tissues. In this study, we determined the extent to which these peripheral tissues can be used as surrogates for DNAm in the brain.

Methods: DNA from blood, saliva, buccal swab and live brain tissue samples from 13 treatment refractory epilepsy patients undergoing brain resection were collected. Genome-wide methylation was assessed with the Infinium HumanMethylation EPIC BeadChip array. Data were analyzed with the R package RnBeads.

Results: Blood, saliva and buccal showed a high degree of correlation for DNAm (r2=0.97), and saliva DNAm was revealed to be more similar to brain DNAm (r2=0.79) than was blood (r2=0.74; p<1x10-4) or buccal swab (r2=0.71; p<1x10-4). However, specific genes showed different correlation patterns. For example, for NR3C1, buccal swab showed highest correlation (r2=0.90) to brain than other tissues (saliva: r2=0.81, blood: r2=0.66).

Conclusions: Genome-wide analysis of DNAm from saliva, blood and buccal swab revealed a high degree of correlation with live brain DNAm within individuals, but saliva was the most highly correlated. However, specific genes showed variable correlations between brain and peripheral tissues.

Supported By: K23MH107654

Keywords: Epigenetics, DNA methylation, Human Brain

58. Experiencing Violence Accelerates Epigenetic Aging in Children

Tanja Jovanovic1, Alexander Vance1, Dorthie Cross1, Anna Knight1, Varun Kilaru1, Vasiliki Michopoulos1, Torsten Klengel2, and Alicia Smith3

1Emory University, 2Harvard University, 3Emory University School of Medicine

Background: Epigenetic processes, including DNA methylation, change reliably with age across the lifespan, such that DNA methylation can be used as an “epigenetic clock”. This epigenetic clock can be used to predict age and age acceleration, which occurs when methylation-based prediction of age exceeds chronological age and has been associated with increased mortality.

Methods: In the current study we examined epigenetic age acceleration data from saliva samples collected from children between ages 6-13 (N=101). Children’s exposure to neighborhood violence was assessed with child report using the VEX-R and heart rate during a stressful startle task was acquired using Biopac. DNA methylation levels were interrogated from saliva using the Illumina HumanMethylation450 BeadChip.

Results: A linear regression controlling for demographic factors, including child sex, parental education, and household income, showed that experiencing violence predicted increased age acceleration (F=9.15, p=0.003). There was also an effect of age acceleration on HR, F=6.59, p=0.002. Post-hoc tests showed that “epigenetically older” children had lower HR compared to other children. These results suggest that age acceleration is associated with decreased HR, similar to HR of adults in this paradigm from our previous studies.

Conclusions: This is the first study to show the effects of direct violence exposure on epigenetic aging in children using salivary DNA. Accelerated epigenetic aging was associated with adult-like cardiovascular function during a stressor. These data suggest that DNA methylation during childhood may be involved in biological mechanisms underlying the relationship between trauma exposure and adverse health outcomes later in life.

Supported By: NARSAD, NIH R01 MH1100122

Keywords: Trauma Exposure, DNA methylation, Heart Rate, children

59. Neurobiological Correlates of PTSD-Related Accelerated Aging

Mark Logue1, Mark Miller2, Regina McGlinchey3, William Milberg3, and Erika Wolf2

1VA Boston Healthcare System, 2Boston University & VA Boston Healthcare System, 3Harvard Medical School & VA Boston Healthcare System

Background: DNA methylation at multiple loci can be used to create a summary profile of cellular age which is strongly...
correlated with chronological age. These cellular age profiles can be used to study exposures and events which are associated with increased cellular age relative to chronological age (accelerated aging).

**Methods:** We examined the predictive strength of trauma and PTSD on measures of cellular age in two separate VA cohorts. We also examine the relationship between accelerated aging and health correlates such as neuronal integrity, neurocognitive functioning, metabolic syndrome, and mortality.

**Results:** In a cohort comprising 281 veterans, latent PTSD severity was associated with accelerated cellular aging ($β = .13, p = .032$). Accelerated cellular age was associated with metabolic syndrome severity ($β = .14, p = .019$) and decreased neural integrity in the genu of the corpus callosum ($β = −.17, p = .009$) which in turn was associated with poorer neuropsychological functioning ($β = −.05, p = .029$). In a second cohort ($n=462$) we found that PTSD hyperarousal symptom severity was associated with accelerated DNA methylation age ($β = .20, p = .009$) in veterans. Further, we observed that every year of increased cellular age was associated with a 13% increased risk of mortality over the period of study follow-up ($p = .029$).

**Conclusions:** These results indicate that PTSD symptoms may be linked to premature health decline that can be measured by DNA methylation indices of cellular age. This may help identify molecular mechanisms associated with poor health outcomes in subjects with PTSD.

**Supported By:** NIMH award # R21MH102834 to MWM and by the Translational Research Center for TBI and Stress Disorders (TRACTS), a VA Rehabilitation Research and Development (B9254-C). Research reported in this publication was also supported by NIA award #RO3AG051877 to EJW and by a Presidential Early Career Award for Scientists and Engineers (PECASE) to Erika Wolf and by U.S. Department of Veterans Affairs (VA) Office of Research and Development (PECASE 2013A). This work was also supported by: NIMH award # R01 MH079806, U.S. Department of VA Clinical Sciences Research & Development Merit Review award # S101CX000431-02, and U.S. Department of VA Biomedical Laboratory Research & Development Program award #1101BX002150-01, all to MWM.

**Keywords:** DNA methylation, PTSD, aging

### 60. Dynamic Patterns of Fear-Associated Gene Expression in the Amygdala and Blood

Alicia Smith1, Adriana Lori2, Stephanie Maddox3, Sumeet Sharma3, Raul Andero4, and Kerry Ressler3

1Emory University School of Medicine, 2Emory University, 3McLean Hospital - Harvard Medical School, 4Autonomous University of Barcelona

**Background:** Identification of the biological responses to fear and stress in both brain and blood is vital for interpreting peripheral studies of psychiatric traits. The goal of this study was to determine which genes are responsive to fear conditioning (FC), an established model of trauma exposure in rodents, under variable levels of stress.

**Methods:** RNA sequencing was performed in blood and amygdala of mice that underwent FC and prior immobilization stress + FC (Immo+FC), a paradigm that induces profound HPA axis and behavioral stress sensitization. Each group consisted of 12 mice pooled into 6 samples for sequencing, and the groups were compared with cuffdiff. DAVID was used to evaluate whether association genes were enriched for biological processes. The FDR was controlled at 5% to account for multiple testing in all analyses.

**Results:** In the amygdala, expression of 516 genes differed between the Immo+FC and FC only groups (FDR<.05). These genes were enriched for relevant biological processes including startle response and associative learning. In the blood of the same animals, expression of 468 genes differed between the Immo+FC and FC only groups (FDR<.05) and were enriched for inflammation and cytokine signaling. Expression of 10 genes associated in the same direction in the blood and amygdala of both groups.

**Conclusions:** This study identified genes and pathways that respond in amygdala and blood to fear in stress-exposed individuals, providing insight into the physiological processes underlying fear disorders. Future studies will be needed to see if they associate with PTSD and other trauma-related disorders in humans.

**Supported By:** NARSAD

**Keywords:** Amygdala, Trauma, Posttraumatic Stress Disorder, RNA-seq, Biomarkers

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### ORAL SESSION

**Clinical/Translational Neuroscience of Psychosis and Related Disorders #1**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM

Aqua 311 AB

Chair: Sanjay Mathew

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**61. Olanzapine Inhibits Central Insulin Action Resulting in Glucose Dysregulation**

Chantel Kowalchuk1, Celine Teo3, Virginia Wilson3, Adria Giacca4, Gary Remington3, and Margaret Hahn1

1CAMH, 2University of Toronto, Institute of Medical Sciences, Canada, 3Centre for Addiction and Mental Health, Toronto, Canada, 4University of Toronto, Physiology

**Background:** Antipsychotics like olanzapine (OLA) are widely prescribed but associated with high rates of type 2 diabetes (T2D). Historically the risk of T2D was attributed to their weight gain propensity. However, existing work shows that: a) independently of weight gain antipsychotics have an immediate effect, and b) they act at least in part via the brain, to perturb glucose homeostasis. Intriguingly, links between central insulin pathways and antipsychotic efficacy have been proposed.

**Methods:** Pancreatic euglycemic clamps were used to measure glucose kinetics (hepatic glucose production (HGP) and disposal), allowing maintenance of basal peripheral insulin levels and separate manipulations of central insulin levels. Rats were pretreated with an acute subcutaneous dose of olanzapine (OLA) or vehicle (VEH) according to our established model of OLA-induced...
insulin resistance. A central infusion of insulin (established to suppress HGP) or VEH was administered into the 3rd ventricle during the clamp. Groups were as follows (central-peripheral): VEH-VEH (n=11); VEH-OLA (n=8); INS-OLA(n=10); INS-VEH (n=10).

**Results:** There were no differences between groups in peripheral glucose or insulin levels. The INS-VEH group demonstrated significant suppression of HGP (clamp relative to basal: 77.9% +/- 13.1; p=0.05), an effect no longer observed when OLA (i.e. INS-OLA: 7.7% +/- 14) was co-administered. Suppression levels were similar across the other groups to INS-OLA; all were all significantly lower vs. INS-VEH.

**Conclusions:** For the first time, we demonstrate that OLA, in vivo, induces hypothalamic insulin resistance. This work is critical to furthering our understanding of a very serious adverse effect, which through the brain may overlap with treatment dimensions of schizophrenia.

**Supported By:** Banting and Best Diabetes Centre (University of Toronto, Canada), Banting Research Foundation

**Keywords:** Second Generation Antipsychotics, Diabetes Mellitus, Intracerebroventricular insulin, Schizophrenia, insulin resistance

62. Acoustic Startle Latency is Prolonged in Schizophrenia in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Cohort

Nicholas Massa1, Arpita Bhattacharya2, John A Sweeney4, Godfrey D Pearson5, Matcheri S Keshavan6, Carol A Tamminga1, Brett A Clementz6, and Erica Duncan1

1Emory University School of Medicine, 2Atlanta VA Medical Center; Emory University School of Medicine, 3University of Washington, 4University of Cincinnati, 5Yale Institute of Living, 6Harvard University, 7University of Texas Southwestern Medical Center, 8University of Georgia

**Background:** Latency of the acoustic startle reflex is the time from the presentation of the startling auditory stimulus until an elicited startle response, and provides an index of neural processing speed. Previous work shows latency is prolonged in schizophrenia compared to controls, is 90% heritable, and predicts conversion to schizophrenia in a high-risk population. The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium investigates endophenotypes found in psychotic disorders spanning diagnostic criteria for schizophrenia and bipolar disorder. Herein we investigated whether prolonged latency occurs in schizophrenia, bipolar disorder subjects, and their families.

**Methods:** 295 subjects were included from the B-SNIP cohort: 77 with schizophrenia/schizoaffective disorder (SCZ), 86 of their family members (SCZ-Fam), 27 bipolar subjects (BP), 25 of their family members (BP-Fam), and 80 controls (CONT). A Biopac system recorded the eyelink component of the startle reflex during startle testing.

**Results:** A stepwise linear regression on latency was significant for SCZ, indicating that latency was prolonged in this group (B=0.007, p=0.01). Latency was not prolonged in BP subjects. In a univariate ANOVA, latency was slowest in SCZ, fastest in CONT, with SCZ-Fam intermediate (F=3.28, p=0.04). A parallel analysis on BP and their families was not significant. Analyses on prepulse inhibition of startle were not significant for SCZ or BP. Slower latency predicted higher negative symptoms in SCZ (B=46.03, p=0.02).

**Conclusions:** Startle latency may be a useful biological probe for genetic contributions to schizophrenia. Future work will examine whether latency predicts psychosis across SCZ and BP biotypes in a larger sample.

**Supported By:** National Institute of Mental Health (MH-077851, MH-077813, MH-077945, MH-077852, MH-077862); NARSAD/Brain & Behavior Research Foundation John Kennedy Harrison Young Investigator Award (17801); Veterans Affairs Merit Review award (CX-000974-01).

**Keywords:** Schizophrenia, acoustic startle latency, prepulse inhibition

63. Cannabinoid-Mediated Disruption of Sensory Gating and Neural Network Oscillations: A Translational Study in Humans and Rats

Patrick Skosnik1, Mihaly Hajos2, Jose Cortes-Briones2, Brian Pittman3, Andrew Sewell2, Deepak D’Souza2, and Mohini Ranganathan2

1Yale School of Medicine, 2Yale University

**Background:** Cannabis use has been associated with altered sensory gating and neural oscillations. However, it is unclear which constituent in cannabis is responsible for these effects, or whether these are cannabinoid receptor (CB1R) mediated. Therefore, the present study in humans and rats examined whether cannabinoid administration would disrupt sensory gating and evoked oscillations utilizing electroencephalography (EEG) and local field potentials (LFPs), respectively.

**Methods:** Human subjects (n=15) completed four test days during which they received intravenous delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), THC+CBD, or placebo. Subjects engaged in a dual-click sensory gating paradigm, and outcome measures included P50 gating ratio (S2/S1) and evoked power to S1 and S2. In order to examine CB1R specificity, rats (n=6) were administered the CB1R agonist CP-55940, CP-55940+AM-251 (a CB1R antagonist), or vehicle using the same gating paradigm. LFPs were recorded from CA3 and entorhinal cortex.

**Results:** Both THC (p<0.007) and THC+CBD (p<0.004) disrupted P50 gating ratio compared to placebo, while CBD alone had no effect. THC (p<0.048) and THC+CBD (p<0.035) decreased S1 evoked theta power, and in the THC condition, S1 theta negatively correlated with gating ratios (r=-0.629, p<0.012). In rats, CP-55940 disrupted gating in both brain regions (p<0.0001), and this was reversed by AM-251. Further, CP-55940 decreased evoked theta (p<0.0077) and gamma (p<0.011) power to S1, which was partially blocked by AM-251.

**Conclusions:** These data suggest that cannabinoid agonists disrupt sensory gating by altering neural oscillations in the theta-band, and that these effects are CB1R mediated. Results are discussed in the context of the perceptual and psychotomimetic effects of cannabinoids.

**Supported By:** R21 DA030696-01

**Keywords:** Cannabis, Cannabinoid, EEG, Neural Oscillations, Sensory Gating
64. The Processing-Speed Impairment in Psychosis is More than Just Accelerated Aging

Samuel Mathias1, Emma Knowles2, Jennifer Barrett3, Olivia Leach3, Sebastiano Buccheri3, Tamara Beetham3, John Blangero4, Russell Poldrack5, and David Glahn6

1Yale School of Medicine, 2Yale University, 3Olin Neuropsychiatry Research Center, 4University of Texas Health Science Center, 5Stanford University

Background: Processing speed is impaired in patients with psychosis, and deteriorates as a function of normal aging. These observations, in combination with other lines of research, suggest that psychosis may be a syndrome of accelerated aging. But do patients with psychosis perform poorly on tasks of processing speed for the same reasons as older adults?

Methods: Fifty-one patients with psychotic illnesses and 90 controls with similar mean IQ (aged 19–69 years, all African American) completed a computerized processing-speed task, reminiscent of the classic digit-symbol coding task. The data were analyzed using the drift-diffusion model (DDM), and Bayesian inference was used to determine whether psychosis and aging had similar or divergent effects on the DDM parameters.

Results: Psychosis and aging were both associated with poor performance, but had divergent effects on the DDM parameters. Patients had lower information-processing efficiency (“drift rate”) and longer non-decision time than controls, and psychosis per se did not influence response caution. By contrast, the primary effect of aging was to increase response caution, and had inconsistent effects on drift rate and non-decision time across patients and controls.

Conclusions: The results reveal that psychosis and aging influenced performance in different ways, suggesting that the processing-speed impairment in psychosis is more than just accelerated aging. This study also demonstrates the potential utility of computational models and Bayesian inference for finely mapping the contributions of cognitive functions on simple neurocognitive tests.

Supported By: NIMH R01MH106324-01

Keywords: Schizophrenia, Processing Speed, Bayesian model, Computational Psychiatry

65. Neurophysiology of Auditory Object Formation Deficits in the First-Episode Schizophrenia Spectrum

Brian Coffman1, Sarah Haigh2, Tim Murphy2, Kayla Ward2, and Dean Salisbury2

1University of Pittsburgh, 2Department of Psychiatry, University of Pittsburgh School of Medicine

Background: Grouping of auditory percepts into objects is necessary for navigating the auditory environment. Long-term schizophrenia patients have reduced neurophysiological responses associated with perceptual grouping, including attenuated N2 and sustained potential (SP). It is unknown whether N2 and SP responses to auditory groups are intact at the first psychotic episode.

Methods: Twenty-three FESz (within 6 months of first psychotic episode) and 23 matched healthy controls (HC) ignored tone groups while watching a silent cartoon. Stimuli comprised 300 groups of three identical tones (1 kHz; 80 dB; 50 ms duration; 330 ms SOA, 800 ms ITI) with rare deviant groups of four tones (not discussed here). N2 and SP were measured to standard groups. Sources of the SP were localized using minimum-norm estimation for the subsets of individuals with structural MRI (FESz = 17; HC = 18).

Results: SP was reduced in FESz compared to HC (p < 0.05). Contrary to findings in long-term schizophrenia, N2 responses were not significantly reduced (p > 0.1). Source analysis revealed that SP was generated in bilateral primary auditory cortex (A1) and dorsal medial frontal cortex (dMFC). Sustained activity in dMFC (p < 0.001), but not A1 (p > 0.1) was reduced for FESz compared to matched controls.

Conclusions: These results suggest that deficits in auditory pattern processing in schizophrenia occur early in the disease course. dMFC activity reductions in FESz may be rooted in salience network dysfunction or other dMFC-related processes, such as predictive model updating. Further work will assess symptom and functioning concomitants in deficits in this fundamental complex perceptual process.

Supported By: NIH R01 MH094328

Keywords: Schizophrenia, Auditory Perception, EEG, N200, Sustained Potential

66. Increased C3 and C4 Proteins in Serum of FEP and UHR Patients: Implications for Inflammatory Subtyping in SCZ

Liliana Laskaris1, Gursharan Chana1, Cynthia Shannon Weickert2, Chad Bousman3, Bernhard Baune4, Patrick McGorry5, Ian Everall6, Chritsos Pantelis5, and Vanessa Cropy5

1University of Melbourne, 2Neuroscience Research Australia, 3University of Adelaide, 4Orygen, National Centre of Excellence in Youth Mental Health, 5Melbourne Neuropsychiatry Centre, 6Melbourne University

Background: The complement system is proposed to undergo changes in schizophrenia (SCZ) depending on illness course and neuro-immune crosstalk. Although studies have reported increased complement proteins in blood of patients, it remains unclear whether these levels change over the course of illness. The aim of this study was to: i) investigate whether complement proteins are altered at different stages of illness and ii) determine the presence or absence of a pro-inflammatory subgroup based on complement levels.

Methods: C1q, C3, C4 from the Human Complement Panel 2 (MPHCMP2MAG-19K-03, Merck Millipore) were quantified in 183 participants [n = 83 Healthy Controls (HC), n = 10 Ultra High Risk (UHR), n = 40 First Episode Psychosis (FEP), n = 50 Chronic SCZ]. Participants were compared relative to their age and gender matched control groups using Mann Whitney test and clustering was performed using a recursive two-step cluster analysis on the entire cohort.

Results: C4 was increased in all SCZ groups. UHR had higher C3 and C4 while FEP had increased C1q, C3 and C4 (p < 0.05) that were significantly correlated with cytokines. Two-step cluster analysis produced a two cluster model, with a chi-square test of independence showing that only FEP were
significantly more likely (48%) to be in the high complement group compared to their respective controls (24%).

**Conclusions:** Our finding indicates complement activity may be particularly increased early in psychosis while the correlation with pro-inflammatory cytokines indicates this may be part of a wider inflammatory process. Future studies will focus on investigating the associations between complement, cytokines and their impact on brain volume.

**Supported By:** NHMRC, RMH

**Keywords:** first episode schizophrenia, complement proteins, inflammation, serum, cytokines

67. Ketamine-induced Changes in Neural Noise and their Relationship to Psychosis-like Symptoms

Jose Cortes-Briones¹, Patrick Skosnik², Deepak D’Souza², Chadi Abdallah³, Ismene Petrakis², and John Krystal²

¹Yale University, ²Yale University School of Medicine

**Background:** The brain is a complex network of nodes exchanging information. Information transfer/processing can be modulated by the relative proportion of signal and noise of neural activity. GABAergic interneurons play a crucial role in modulating signal-to-noise ratio (SNR) in neural circuits. By disrupting SNR, the GABAergic deficits of schizophrenia may disrupt information transfer/processing and lead to psychotic symptoms. The NMDAR antagonist ketamine produces an array of psychotomimetic effects. It is argued that by blocking NMDARs located in GABAergic interneurons, ketamine mimics aspects of the GABAergic deficits of schizophrenia. This study assessed the effects of ketamine on neural noise and SNR, and their relationship to psychosis-like symptoms.

**Methods:** In this double-blind, placebo-controlled study, 81 healthy subjects received subanesthetic doses of ketamine (0.23mg/kg loading, rate 0.58mg/kg.h) and performed an oddball P3b EEG task. Baseline noise (signal randomness) was measured with the Lempel-Ziv Complexity (LZC) of the baseline period; SNR was calculated for the ERP interval.

**Results:** Ketamine increased baseline LZC, reduced both P3b peak amplitude and SNR, and increased CADSS scores (all ps<0.05). LZC was negatively correlated with both peak amplitude and SNR (rho=−0.36 and -0.53, respectively), also, peak amplitude and SNR were positively correlated (rho=0.69). CADSS scores were positively correlated with LZC (rho=0.37) and negatively correlated with both SNR (rho=0.45) and peak amplitude (rho=−0.54).

**Conclusions:** Ketamine disrupted neural activity’s equilibrium between signal and noise. Increased noise and reduced SNR may disrupt neural networks’ information transfer/processing, leading to the psychotomimetic effects of ketamine. These findings may help to clarify the mechanisms underlying psychotic symptoms in schizophrenia.

**Supported By:** VA; National Institute on Alcohol Abuse and Alcoholism (National Institute on Alcohol: Abuse and Alcoholism)

**Keywords:** Ketamine, Schizophrenia, Brain networks, Entropy and complexity, GABA deficit

68. Interhemispheric Paired Associative Stimulation of the Prefrontal Cortex Induces Acute Cognitive and Electrophysiological Alterations

Samuel Zibman, Edan Daniel, Uri Alyagon, and Abraham Zangen

Ben Gurion University

**Background:** Interhemispheric paired associative stimulation (PAS) is an emerging protocol for TMS that can potentially target connectivity across hemispheres. Yet, most studies have thus far been limited to the motor cortex. We set out to evaluate potential electrophysiological and behavioral modifications following PAS between the right and left prefrontal cortex (PFC) that are dependent on the direction in which PAS is administered, i.e., which hemisphere is stimulated first.

**Methods:** Twenty seven subjects were recruited for a three session, sham-controlled crossover study, receiving left to right PAS (LR-PAS), right to left PAS (RL-PAS) and sham during different weeks. The protocol consisted of 210 pulse pairs with an ISI of 8ms. Subjects performed the emotional Stroop task, assessed by measuring attentional bias, and brain activity was recorded with EEG prior to and following the stimulation period.

**Results:** PAS induces an increase in interhemispheric signal propagation only in the direction of the PAS protocol (left to right for LR-PAS and right to left for RL-PAS) and not in the reverse direction (3-way ANOVA F(2,27) = 3.15, p < 0.05 ). Additionally, this change in connectivity is associated with a behavioural change. LR-PAS increased attentional bias whereas RL-PAS decreased it (2-way ANOVA F2, 27 = 3.266, p < 0.05).

**Conclusions:** This is the first demonstration of PAS’s effectiveness in inducing cognitive changes by targeting interhemispheric PFC connectivity in a directional manner. Furthermore, by combining TMS-PAS with EEG, we provide a toolbox for evaluating the effectiveness of PAS protocols currently being developed as novel treatment strategies.

**Supported By:** The MAGNET program of the Israeli OCS as part of the Brain Stimulation and Monitoring Technique (BSMT) consortium.

**Keywords:** Deep TMS, TMS-EEG, Paired Associative Stimulation, Neuromodulation, Emotional processing

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**ORAL SESSION**

**Clinical Neuroscience of Mood Disorders**

**Thursday, May 18, 2017, 3:00PM - 5:00 PM**

**Aqua 310 AB**

Chair: James Murrough

69. Neuroactive Steroids and GABA in Peripartum Depression

Kristina Deligiannidis³, Scott Shaffer², Aimee Kroll-Desrosiers³, Elf Sitoglu⁴, Abby Syenson⁵, Nina Jaitly⁶, Vanessa Villamarin⁵, Shunyan Mo⁷, Hien Nguyen⁷, Janet Hall⁸, Blaise Frederick⁹, Richard Edden¹⁰, Constance Moore⁹, and Anthony Rothschild⁹

**Keywords:** GABA, Pro-inflammatory cytokines, Schizophrenia, Neuropeptides, Peripartum Depression
70. Cortical Inhibition as a High Potential Biomarker of Response across Brain Stimulation Modalities in Treatment Resistant Depression

Daphne Voineskos 1, Daniel M. Blumberger 2, Yinning Sun 3, Nigel Rogasch 4, Reza Zomorrodii 5, Faranak Farzan 2, Tarek Rajji 2, and Zafiris J. Daskalakis 2

1University of Toronto and CAMH, 2Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto; University of Toronto, 3Centre for Addiction and Mental Health, 4Monash University, Melbourne, 5Center for Addiction and Mental Health, 6Centre for Addiction and Mental Health, University of Toronto

Background: The gold standard of therapy in Treatment Resistant Depression (TRD) is brain stimulation. However, there has previously been no defined biological marker to predict or understand therapeutic response to brain stimulation. Dysfunctional cortical inhibition (CI) has been postulated as a mechanism through which MDD symptoms are mediated. Our lab has conducted several investigations in cortical inhibition (CI), utilizing investigational TMS to understand response across brain stimulation therapies (ECT, rTMS and MST).

Methods: 25 patients underwent TMS-EMG CI paradigms before and after ECT. 30 patients underwent TMS-EEG CI paradigms before and after rTMS. 27 patients underwent TMS-EEG CI paradigms before and after MST. All patients were diagnosed with TRD. TMS-EMG CI paradigms included the cortical silent period (CSP). TMS-EEG CI paradigms included N100 response and LICI. Baseline TMS measures were assessed within 1 week prior to the initiation of acute brain stimulation and post-TMS measures within 48h of the final treatment.

Results: In ECT subjects, baseline CSP predicted therapeutic response to ECT with sensitivity of 80% and specificity of 60%. In rTMS subjects, a strong correlation appeared between Δ N100 Amplitude and Δ HDRS (r = 0.63, p = 0.002) in the active rTMS group. In MST subjects, N100 and LICI predicted remission of suicidal ideation with 90% sensitivity and 89% specificity.

Conclusions: Our results suggest cortical inhibition has high potential in TRD as a biomarker of response across brain stimulation therapies. These findings suggest that stronger inhibitory neurotransmission at baseline reflects the integrity of interneuronal networks, optimal targets for brain stimulation therapy in TRD.

Keywords: Treatment Resistant Depression, Brain Stimulation, Cortical Inhibition, Biomarkers

71. Improving the Regional Specificity of CNS Drugs by Targeting Accessory Proteins: Proof-of-Concept Using Glutamate Receptors

Michael Maher, Nyantsz Wu, Suchitra Ravula, Michael Ameriks, Brad Savall, Brian Lord, Jose Matta, Nicholas Carruthers, and Timothy Lovenberg

Janssen Research and Development
Background: Mood disorders can be considered as imbalances in the activity of specific neuronal circuits. The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of ionotropic glutamate receptors mediates the majority of fast synaptic transmission within the mammalian brain. The ubiquitous expression of the primary subunits of AMPA receptors (AMPARs), and the lack of pharmacological selectivity amongst them, preclude regional or neuronal subtype specificity. In vivo, AMPARs comprise a variety of accessory proteins. Of particular interest, TARPs-gamma8 is highly expressed in the hippocampus, part of the limbic circuitry that putatively is overactive in recurrent mood disorders.

Methods: We used high-throughput screening to discover compounds that selectively modulate AMPARs containing TARPs-gamma8. Subsequent medicinal chemistry efforts were used to improve potency and pharmacokinetics of the hits. Assays were developed to measure target occupancy and functional effects of the compounds in vivo.

Results: These compounds possess a novel mechanism-of-action consistent with a partial attenuation of the interaction between the TARPs and the pore-forming subunits of the channel. Lead molecules with oral bioavailability and high brain penetration allowed demonstration of a strong relationship between pharmacokinetics and pharmacodynamics. The compounds show anticonvulsant and anxiolytic profiles in rodent. Molecules in this class provide large safety margins relative to non-specific AMPAR inhibitors due to the improved regional specificity of TARPs-gamma8 modulators.

Conclusions: AMPAR modulators selective for TARPs-gamma8 have the potential to be novel treatments for anxiety/depression, bipolar disorder, temporal lobe epilepsy, and/or prodomal schizophrenia. This project also represents proof-of-concept for pharmacological targeting of accessory proteins and small-molecule modulation of protein-protein interactions.

Keywords: ionotropic glutamate receptors, Pharmacology, Mood disorders, anticonvulsants, Hippocampus

72. Light Therapy for Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial of Bright White versus Dim Red Light for Bipolar Depression

Dorothy Sit1, James McGowan2, Christopher Wiltrout2, Rasim Somer Diler2, John (Jesse) Dills3, James Luther3, Howard Selitman4, Stephen Wisniewski5, Michael Terman5, and Katherine L Wisner1

1Northwestern University, Feinberg School of Medicine, 2University of Pittsburgh Medical Center, 3University of Pittsburgh, Graduate School of Public Health, 4Carnegie Mellon University, Department of Statistics, 5Columbia University, New York State Psychiatric Institute

Background: Patients with Bipolar Disorders (BD) have recurrent major depression, residual mood symptoms, and limited treatment options. We conducted a 6-week, double-blind, parallel, placebo-controlled trial to investigate the efficacy of midday bright light therapy for bipolar depression. The aims were to determine remission rates, depression severity, and the rate of mood polarity switch in patients randomized to 7000-lux bright white or 50-lux dim red light.

Methods: We enrolled depressed adults with BD Type-I or II and receiving stable-dosed antimanic medication. We excluded patients with hypomania, mania, mixed symptoms or rapid cycling. We assessed mood symptoms weekly with the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement, the Mania Rating Scale. Remission was defined by a SIGH-ADS ≤ 8. Patients used the assigned study light box at home or work, starting with 15-minutes daily at midday (12:00-2:30 PM). The light-dose was increased by 15-minutes every week until target dose of 60 minutes at Week 4 unless remission was attained.

Results: We randomized 23 to bright white and 23 to dim red light. At baseline, both groups had moderate depression severity and no hypomanic symptoms. At Week 6, the group randomized to bright white compared to dim red light had a significantly higher remission rate (56.5%, 13/26 versus 14.3%, 3/26; adjusted odds ratio=6.0, p=0.03) and significantly fewer depressive symptoms (10.3±8.2 versus 17.9±9.6 adjusted β=−6.066, p=0.02). No mood polarity switch was observed.

Conclusions: Findings provide robust evidence which confirms the efficacy of midday bright light therapy for bipolar depression.

Supported By: National Institute of Mental Health, K23 MH 082114, Career Development Award, PI – D. Sit; The Brain and Behavioral Research Foundation, NARSAD 2013 Young Investigator Grant, PI – D. Sit; Uplift Technologies, Inc. for their donation of study light boxes for use in the K23 research study; and Department Funds from the University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Chair, Dr. David Lewis, M.D.

Keywords: bipolar depression, Light Therapy, Clinical Trials, Novel Intervention, Bipolar Disorder

73. Efficacy of Transcranial Direct Current Stimulation in Unipolar and Bipolar Depression: Results from an International Randomized Controlled Trial

Colleen Loo1, Sarah Lisanby2, Mustafa Husain3, William McDonald4, Scott Aaronson5, John O’Reardon6, Donel Martin1, Angelo Alonzo7, Shawn McClintock8, and Cynthia Shannon Weickert9

1University of New South Wales, 2Now at the National Institute of Mental Health. Dr. Sarah H. Lisanby contributed to this article while at Duke University, prior to joining NIMH. The views expressed are her own and do not necessarily represent the views of the National Institutes of Health or the United States Government, 3UT Southwestern Medical Centre, 4Emory University, 5Sheppard Pratt Health System, 6Now at Psychiatry at the Pavilions. Dr O’Reardon contributed to this study while at the University of Medicine & Dentistry of New Jersey, 7School of Psychiatry UNSW, 8The University of Texas Southwestern Medical Center, Department of Psychiatry, 9Neuroscience Research Australia

Background: Evidence suggests transcranial Direct Current Stimulation (tDCS) has antidepressant efficacy. Large, well designed trials are required to confirm efficacy, and further assess safety, including in bipolar depression. Prior research
suggests BDNF Val66Met genotype moderates response to anodal tDCS.

**Methods:** 130 participants (91 unipolar, 39 bipolar) with DSM IV Major Depressive Episode were randomized to receive active (2.5 mA, 30 minutes) or sham (34 microamperes and two 60-second current ramps up to 1 and 0.5 mA) left prefrontal tDCS, 20 sessions over four-weeks, in a double-blinded, multisite study. Mixed effects repeated measures analyses assessed change in mood and neuropsychological scores, with diagnostic group (unipolar, bipolar) and BDNF Val66Met genotype (n=94) as factors.

**Results:** Mood improved significantly over the 4-week treatment period (p<0.001). No differences were found between active and sham treatment except in bipolar participants, who improved more after sham stimulation (p=0.003). BDNF genotype also influenced outcomes, with val/val homozygotes improving more after sham stimulation (p<0.001) and met allele carriers improving more with active stimulation (p<0.001).

**Conclusions:** Overall, active tDCS was not more effective than sham stimulation. It is possible that the minimal stimulation delivered during 30 minutes sham tDCS, repeated over 20 sessions, had biologically active effects, evident in those with bipolar depression and val/val BDNF homozygotes, indicating a possibility these groups may be more responsive to low levels of stimulation. Future research should assess dose–response relationships accounting for diagnostic groups and BDNF genotype.

**Supported By:** Stanley Medical Research Foundation

**Keywords:** transcranial Direct Current Stimulation, Major Depression, Efficacy, BDNF Val66Met, Bipolar Disorder

74. PERSEVERE: A Study of Esketamine for the Reduction of the Symptoms of Major Depressive Disorder, including Suicidal Ideation, in Subjects Assessed to Be at Imminent Risk for Suicide

Carla Canuso1, Jaskaran Singh1, Maggie Fedgchin1, Larry Alphs2, Roseanne Lane1, Pilar Lim1, Christine Pinter1, Abdul Sankoh1, and Helen Colquhoun1

1Janssen Research & Development, LLC, 2Janssen Scientific Affairs, LLC, 3Janssen Pharmaceutical Research & Development

**Background:** The delayed onset of action of conventional antidepressants significantly limits their utility for treatment of patients at risk of suicide.

**Methods:** PeRSEVERE, a 12-week, randomized, double-blind, placebo-controlled study of investigational intranasal esketamine in subjects with MDD at imminent risk for suicide was designed to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo for reducing the symptoms of MDD including SI.

**Results:** Of the 68 patients randomized, 49 (ESK: 27; placebo: 22) completed the DB treatment phase. Mean (SD) baseline MADRS total scores were: 38.5 (6.17) and 38.8 (7.02) for the ESK and placebo groups, respectively. Change from baseline in MADRS total score was significantly greater for ESK treatment vs placebo (p=0.015) at 4 hours postdose (p=0.015) and 24 hours (p=0.015). A greater proportion of patients in ESK group achieved resolution of suicide risk (CG-JSR score of 0 or 1) vs placebo at 4 hours (21.2% vs 9.7%) and day 2 (40% vs 6.5%). The response rate at day 2 was higher in ESK group (54.3%; 19/35) vs placebo group (29%). Similarly, the remission rate at day 2 was higher for patients treated with ESK (34.3%) vs placebo (16.1%). Treatment with intranasal ESK 84 mg was generally tolerated with side effects that included temporary perceptual distortion and modest increase in blood pressure.

**Conclusions:** The study provides useful information for the safety and efficacy of intranasal ESK in patients with MDD assessed to be at imminent risk for suicide, but further investigation is need to establish its clinical utility.

**Keywords:** esketamine, major depressive disorder, suicidal thinking

75. A Single-Ascending Dose Study of the Neuroactive Steroid SAGE-217

Stephen Kanesh1, George Nomikos1, Michael Quirk1, Shane Raines2, James Doherty1, Ethan Hoffmann1, Abdul Sankoh1, and Helen Colquhoun1

1Sage Therapeutics, Inc, 2b Analytics

**Background:** SAGE-217 is a novel, proprietary, positive allosteric modulator of synaptic and extrasynaptic GABA receptors developed from the neuroactive steroid scaffold to be administered orally. It is currently being investigated for its potential use in multiple indications with GABA-related etiology, including postpartum depression and essential tremor.

**Methods:** Seventy-two healthy volunteers were enrolled in a Phase 1, double-blind, placebo-controlled single-ascending dose study of SAGE-217. Subjects were randomized 6:2 to a single dose of SAGE-217 oral solution or placebo. Dosing was escalated from 0.25 mg to 66 mg in nine different cohorts until the maximum tolerated dose (MTD) was achieved based on pre-specified stopping criteria, mainly related to sedation. Electroencephalogram (EEG) recording was used to assess target engagement (GABAA receptor modulation) in the brain by measuring changes in electrical activity following SAGE-217 administration.

**Results:** SAGE-217 was generally well tolerated, and most adverse events were reported as mild or moderate. No serious adverse events were reported. The MTD was identified as 55 mg daily based on the predefined Modified Observers Assessment of Awareness/Sedation (MOAA/S) stopping criterion, and EEG recordings showed evidence of target engagement at doses below the MTD. At the predicted pharmacologically active doses, observed sedation was mild, transient, and associated with peak exposure. Pharmacokinetics results support once daily administration.

**Conclusions:** In this Phase 1 clinical trial, SAGE-217 was generally well tolerated, supporting further development as a potential therapy for multiple indications related to GABA dysfunction. A Phase 2 clinical program has been initiated.

**Supported By:** Sage Therapeutics, Inc.

**Keywords:** neuroactive steroid, GABA, positive allosteric modulation, Postpartum Depression
76. Alks 5461: A Buprenorphine-Samidorphan Combination for Major Depression
Elliot Ehrich, Sanjeev Pathak, William Martin, Asli Memisoglu, Arielle Stanford, and Lauren DiPetrillo
Alkermes, Inc.

**Background:** Growing scientific evidence demonstrates that opioid system modulation holds promise in the therapeutics of major depressive disorder (MDD). However, development of opioids to treat MDD has been problematic due to the risk of abuse. To address the endogenous opioid dysregulation while avoiding abuse and addiction, we studied ALKS 5461, a combination of buprenorphine, a μ partial-agonist with low intrinsic activity and samidorphan, a potent, sublingually-bioavailable μ antagonist.

**Methods:** Building upon previously reported results, we present results of a Phase III study (FORWARD-5) and results of prospectively planned pooled analysis of two Phase III studies (FORWARD-4 and FORWARD-5). Both studies utilized the Sequential Parallel Comparison Design. Enrolled patients had MDD and inadequate response to antidepressants. FORWARD-5 evaluated adjunctive 2mg/2mg and 1mg/1mg. Pooled FORWARD-4 and FORWARD-5 evaluated 2mg/2mg.

**Results:** FORWARD-5 (n=407) demonstrated that 2mg/2mg was superior to placebo in improving core symptoms of depression (MADRS-6; p=0.018), and overall symptoms of depression (MADRS-10; p=0.026). The 1mg/1mg dose showed numerical improvement versus placebo that was not statistically significant. ALKS 5461 was generally well tolerated. The most common adverse events (AEs) were nausea, dizziness and fatigue. There was no pattern of AEs indicative of abuse potential. Furthermore, the pooled analysis of FORWARD-4 and 5 (N=792) demonstrated that 2mg/2mg was superior to placebo in improving both the core and overall symptoms of depression (MADRS-6; p<0.001; MADRS-10, p=0.005).

**Conclusions:** ALKS 5461 provides a novel mechanism in the pharmacotherapy of MDD with “balanced” agonist-antagonist opioid modulation.

**Supported By:** Alkermes, Inc.

**Keywords:** Depression, Treatment Resistance, Randomized Control Trial, mu opiate receptor, kappa opiate receptor

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**SYMPOSUM**

**From Mechanisms to New Medicines: Modeling and Targeting Interneuron Dysfunction**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM
Sapphire AB
Chair: Oliver Howes

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77. Enhancing PV Interneuron Function through Targeted Modulation of Kv3 Channels
Charles Large1, Daniela Cardinu2, Mike Harte2, Tamara Modebadze3, Fiona LeBeau3, Giuseppe Alvaro1, Mark Cunningham3, and Joanne Neill2
1Autifony Therapeutics Limited, 2University of Manchester, 3Newcastle University

**Background:** Evidence supports a central role for parvalbumin (PV) positive interneurons in the pathophysiology of schizophrenia. Kv3.1 potassium channels are selectively expressed by PV interneurons, where they regulate fast firing, essential for network synchronisation and cognitive processing. AUTO00206 is a first-in-class positive modulator of Kv3.1 channels that is in clinical development for the treatment of schizophrenia.

**Methods:** Adult female Lister-Hooded rats received phencyclidine for 7 days (scPCP), followed by 6 weeks washout. Enduring deficits in cognitive task performance and social behaviours were then observed in these animals. Kainate/carbachol-induced fast (20-80 Hz) network oscillations were induced in cortical slices prepared from scPCP rats and in slices of human neocortex obtained from patients undergoing elective brain surgery.

**Results:** AUTO00206 (10-60 mg/kg) significantly restored cognitive and social behavioural deficits induced by scPCP. When administered for 21 days, the drug consistently reversed the deficit in the NOR. This was accompanied by an increase in PV interneuron density in hippocampus and infralimbic cortex (P<0.05). Efficacy of AUTO00206 was also observed after sub-chronic treatment with haloperidol (P<0.05). In vitro, AUTO00206 significantly enhanced the power of fast network oscillations in cortex from scPCP treated rats, but had no effect in slices taken from vehicle treated animals. AUTO00206 also enhanced gamma oscillations in human neocortical slices treated with PCP, but had no effect in the absence PCP.

**Conclusions:** These data support the potential of AUTO00206 to enhance PV interneuron function, improve cortical network synchrony, and treat cognitive and perhaps negative symptoms of schizophrenia.

**Supported By:** These studies were funded by Autifony Therapeutics Limited, by Innovate UK, and the Medical Research Council.

**Keywords:** parvalbumin interneurons, cognition, Schizophrenia, Gamma oscillation, Kv3.1

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78. Stem Cell Derived Interneuron Transplants Reverse Schizophrenia-Like Deficits in a Rodent Model
Dan Lodge
UT Health Science Center At San Antonio

**Background:** A deficit in inhibitory interneuron function is a consistent observation in postmortem studies as well as in
rodent models of schizophrenia. Given that these deficits appear to be primarily limited to parvalbumin (PV) and somatostatin (SST) interneuron subtypes, we tested the hypothesis that restoring PV- or SST- interneuron function would reverse behavioral and neurophysiological deficits in a developmental disruption rodent model of schizophrenia.

**Methods:** Pregnant rats were injected with MAM (22 mg/kg, i.p.) on gestational day 17. To generate enriched populations of interneurons, we used a dual-reporter mouse embryonic stem cell line. Cells were grown in culture, sorted by flow cytometry, then injected into the vHipp of MAM or control rats. Thirty days after transplantation, we examined behavioral and neurophysiological alterations.

**Results:** Here we demonstrate that stem cell derived interneuron transplants integrate within the hippocampal circuitry and reduce aberrant pyramidal cell firing in a rodent model of schizophrenia. This resulted in downstream normalization of dopamine neuron firing, a deficit likely associated with positive symptoms of the disease. Despite similar physiological effects, the PV- and SST-enriched transplants produced dramatically different effects on behavior. Both cell types attenuated deficits in reversal learning and latent inhibition, whereas only PV-positive transplants reversed deficits in set-shifting and social interaction.

**Conclusions:** The data presented here suggest that restoring PV interneuron function in the vHipp may be an effective treatment strategy for schizophrenia to improve not only positive, but also negative and cognitive symptoms of the disease.

**Supported By:** NIMH R01 & Owens Foundation

**Keywords:** parvalbumin interneurons, Stem Cell, Schizophrenia, Animal Model, Dopamine

79. The Effects of Repeated NMDA Blockade with Ketamine on Dopamine and Glutamate Function

Oliver Howes¹ and Michelle Kokkinou²

¹CSC Hammersmith Hospital and Institute of Psychiatry, ²CSC Hammersmith Hospital

**Background:** The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine induces psychotomimetic symptoms and has also been shown to have a rapid antidepressant action. However, the effects of repeated ketamine on translational imaging measures of glutamatergic and dopaminergic function are unknown.

**Methods:** Experiment 1: Ketamine users and controls received MRS imaging of anterior cingulate cortex glutamate. Experiment 2: Mice received repeated ketamine (30mg/kg i.p) or vehicle over 5 days before wash-out and then behavioural testing and a PET scan. 3,4-dihydroxy-6-[(18)F]fluoro-l-phenylalanine to index striatal Ki (dopamine synthesis capacity). Experiment 3: a chemogenetic (DREADD) approach was used to selectively manipulate midbrain dopamine neurons. Gi-coupled (hM4Di) inhibitory receptors were selectively expressed in midbrain dopamine neurons and were activated using CNO to inhibit dopamine neuron firing. These mice received repeated ketamine preceded by either CNO or vehicle. Following a wash-out animals received behavioural testing and a PET scan.

**Results:** Ketamine users showed increased levels of psychotic-like symptoms (effect size d=1.5, p=0.003), but no difference in glutamate/creatine levels (mean (sd) ketamine= 1.55, control=1.52, p=0.7). Ketamine significantly increased locomotor activity in mice (p<0.001) and striatal Ki relative to controls (effect size d=1.3, p<0.05). Striatal Ki was positively correlated with locomotor activity (r=0.6, p<0.05). CNO inhibited the ketamine-induced increase in locomotor activity (p<0.001) and striatal Ki (p<0.05).

**Conclusions:** Repeated ketamine leads to increased striatal dopamine synthesis capacity that is similar in magnitude to that seen in schizophrenia, but is not associated with detectable changes in glutamate levels. The striatal dopamine effects of ketamine require midbrain dopamine neuron activation.

**Supported By:** MRC

**Keywords:** NMDA, Ketamine, Dopamine, Glutamate, Brain Imaging

80. Theories on the Mechanism of Action of Ketamine: From NMDA Receptor Inhibition to the (2R,6R)-HNK Metabolite

Carlos Zarate¹, Todd Gould², Panos Zanos², and Rodrigo Machado-Vieira¹

¹National Institute of Mental Health, ²University of Maryland Baltimore

**Background:** Over the last decade, numerous controlled studies have described rapid, robust, and relatively sustained antidepressant effects of ketamine. However, because of the concerns of side effects and abuse potential with ketamine, efforts are underway to develop similarly rapid acting antidepressants that are better tolerated.

**Methods:** Research has attempted at a cellular and molecular level to better characterize the neurobiological processes/mechanism of action (MOA) implicated in the rapid antidepressants of ketamine following NMDA blockade, the immediate step. In order to better understand the MOA of ketamine, we conducted behavioral, electroencephalographic, electrophysiological and cellular experiments in mice with (R,S)-ketamine and (2S,6S;2R,6R)-hydroxynorketamine (HNK) the byproduct of (R,S)-ketamine’s metabolism.

**Results:** Convergent evidence from behavioral, cellular and molecular studies supports the theory that enhanced AMPAR activity with increase in synaptic plasticity is critical to ketamine’s MOA. In addition, a number of other targets have been implicated in ketamine’s MOA including mTOR, eEF2, GSK-3, α7-nAChR, HDAC5, BDNF, and intracellular mechanisms. More recently we found that the ketamine metabolite (2R,6R)-HNK exerts behavioral, electrophysiological, and cellular antidepressant-related actions in mice, and does not bind to or inhibit NMDARs (Zanos et al. Nature 2016).

**Conclusions:** Convergent data suggests that enhancing AMPA activity with an increase in synaptic plasticity is critical to the MOA of ketamine. In this lecture, I will review the evolution of the theories of ketamine’s MOA from the initial NMDAR hypothesis culminating in data from our recent study with (2R,6R)-HNK as being an NMDAR independent mechanism.
**Supported By:** National Institute of Mental Health  
**Keywords:** AMPA, Ketamine, NMDA Receptor, Metabolism, mechanism of action

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**SYMPOSIUM**

**Results from the OPTICS Project: Janssen Clinical Trial and NIH Data Together, an Open-Science Collaboration**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM  
Sapphire EF  
Chair: Marsha Wilcox

**81. The OPTICS Project: Janssen Clinical Trial and NIH Data Together in an Open-Science Collaboration**

Marsha Wilcox and Adam Savitz  
Janssen

**Background:** The OPTICS Project is an initiative designed to provide a forum for truly open, translational science in schizophrenia. The project uses Janssen paliperidone clinical trials and NIH data from related studies and trials (dbGaP/ NIMH).

**Methods:** The aim of this project is to demonstrate the value of an open-science approach using pharmaceutical clinical trial (CT) and publicly funded (PF) data together to:
1. Advance understanding efficacy and safety of schizophrenia medicines;
2. Increase understanding of schizophrenia disease natural history, subtypes, and etiologies;
3. Develop/extend design and analytic methods for these questions

**Results:** This effort is distinct from other initiatives: it is a time-limited proof of concept for an open-science analytic collaboration; it is not the development of a data resource to be used in perpetuity. The project is governed by a Scientific Advisory Board (Yale, Harvard, Rutgers, NIMH, Janssen). Researchers addressed study objectives using combined CT and PF data. Harvard Catalyst (NCATS) has funded some researchers. Of note, all IP generated by this project is dedicated to the public; free for all to use. All results passing peer review will be published in an open-access online journal. Finally, the pilot will be evaluated with the goal of replicating it for other neuropsychiatric disorders and Janssen compounds.

**Conclusions:** This is the first time pharmaceutical CT and PF data about schizophrenia are being made available to researchers in one place. The ability to analyze these datasets together has enabled researchers to address questions about the disease, therapies, and analytic methods in ways not possible before now.

**Keywords:** Schizophrenia, Clinical Trials, NIH, Methods, Collaboration, Open Science

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**82. Explaining Comparative Efficacy of Antipsychotic Medications: A Causal Mediation Approach**

Linda Valeri¹, Andrea Bellavia², Franca Centorrino³, John Jackson³, and Garrett Fitzmaurice¹

¹Harvard Medical School McLean Hospital, ²Harvard School of Public Health, ³Johns Hopkins Bloomberg School of Public Health

**Background:** There is still debate on whether first and second generation antipsychotics differ in efficacy and in effectiveness. We investigate the interplay of intermediate factors that can explain antipsychotics effects on negative symptoms.

**Methods:** In a comparative effectiveness trial of four atypical antipsychotics vs. perphenazine over 18 months in 1432 patients (Clinical Antipsychotic Trial of Intervention Effectiveness), we use multivariable regression analysis to compare drug effects on a primary outcome, PANSS negative symptoms and on secondary outcomes: PANSS positive and weight-gain. We then employ novel causal mediation analysis approaches to quantify how much of the relative efficacy on negative symptoms is due to the mediating and interactive role of the secondary outcomes.

**Results:** Regression analyses show no difference between olanzapine and perphenazine in negative symptoms at 9 months. Olanzapine displays higher weight-gain (beta = 2.28, CI = 1.56, 2.99) and positive symptoms (beta = 0.79, CI = -0.20, 1.80) at 3 months relative to perphenazine. Regression models for PANSS negative adjusting for treatment, mediators, and confounders yield a positive relationship between secondary and primary outcomes (weight-gain: beta = 0.36, CI = 0.11, 0.61; PANSS positive: beta = 0.22, CI = 0.04, 0.40) and a weight-gain treatment negative interaction (beta = -0.36, CI = -0.68, -0.05). Mediation analyses reveal that assignment to olanzapine vs perphenazine leads to worsening of negative symptoms through the secondary outcomes (IE = 0.28, CI = -0.40, 0.91) and to improvement in symptoms through other pathways (DE = -0.27, CI = -1.60,1.05).

**Conclusions:** Augmented treatment strategies targeting weight-gain and positive symptoms are critical to improve negative symptoms.

**Supported By:** Harvard Catalyst OPTICS pilot grant

**Keywords:** Clinical Trials, Negative Symptoms, Mediation Analysis, Second Generation Antipsychotics, Schizophrenia

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**83. Network Meta-Analysis of Causal Dose-Response Relationships Using Individual Participant Trial Data**

Sharon-Lise Normand³, Jacob Spertus², and Marcela Horvitz-Lennon³

¹Harvard Medical School and Harvard T.H. Chan School of Public Health, ²Harvard Medical School, ³Rand Corporation and Cambridge Hospital

**Background:** People with schizophrenia have higher risk for metabolic morbidity (obesity, dyslipidemia, and diabetes), all risk factors for cardiovascular disease. Second generation antipsychotics increase metabolic risks. Traditional intention-to-treat analyses in clinical trials provide valid inferences regarding average safety and efficacy but a regression of outcome on observed cumulative drug exposure is not causal.

**Methods:** We exploit advances in causal inference and network meta-analysis to better understand the relationship between duration of exposure and outcomes. We analyze the causal effect of cumulative exposure on clinically significant weight gain,
a binary safety outcome for placebo-controlled and active treatment trials. Using randomization as an instrument, we estimate exposure-response curves for participants. We will combine the treatment-exposure curves via network meta-analysis using individual participant data that (a) permit assessment of evidence compatibility from direct and indirect comparisons; (b) separate within from between-trial effects; and (c) bolster conclusions within subgroups. We use the placebo arms of no exposure as the outcome of zero exposure in active treatment arms.

**Results:** We have 15 clinical trials involving 7100 adults with schizophrenia: all trials had paliperidone arms, 3 had risperidone arms, 4 had olanzapine arms, 1 had a quetiapine arm, and 14 had placebo arms. Total cumulative SGA exposure ranged from 6 to 53 weeks. Adherence rates (percentage of total allocated pills taken) varied substantially by drug and patient characteristics, and predictive of weight gain.

**Conclusions:** Methodology for estimation of causal dose-response curves from randomized trials using individual participant data can help reduce bias and uncertainty in dose-response safety assessments.

**Supported By:** 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 TR000110) and financial contributions from Harvard University and its affiliated academic healthcare centers. 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. This study, carried out under YODA Project #2015-0678, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C.

**Keywords:** Clinical Trials, Meta-analysis, Dose Response, causal inference

### SYMPOSIUM

**The Psychiatric Genomics Consortium: Path to Integration of Multi-System Markers of Risk for PTSD**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM
Sapphire IJ
Chair: Caroline Nievergelt
Co-Chair: Rajendra Morey

**85. SNP-Based Dissection of PTSD from Large-Scale Genome-Wide Association Studies (GWAS) across Military and Civilian Cohorts**

Adam Maihofer1, Laramie Duncan2, Andrew Ratanatharathorn3, Shareefa Davies4, Alicia Martin5, Mark Daly5, Kerry Ressler6, Israel Liberzon7, Karestan Koenen8, Caroline Nievergelt9, and PGC PTSD Workgroup10

1Department of Psychiatry, UCSD School of Medicine, 2Stanford University, 3Columbia University, 4University of Cape Town, 5Broad Institute, 6Harvard School of Medicine, 7University of Michigan, 8Harvard School of Public Health, 9University of California San Diego

**Background:** The development of post-traumatic stress disorder is influenced by both genetic and environmental factors. The Psychiatric Genomics Consortium (PGC) PTSD group has the goal to assemble genomic data from 25,000 PTSD cases and 50,000 trauma-exposed controls to conduct the largest GWAS of PTSD to date. Here we present our current findings, including >35 cohorts of diverse ancestry and trauma types.

**Methods:** Over 15,000 PTSD cases and 30,000 controls were included in our current analyses. Genotypes were processed with a modified PGC-pipeline for ancestry assessment. Each
subject’s ancestry was determined and GWASs were performed for each study and ancestry group and meta-analyzed across studies. Standard methods were used to estimate SNP-based heritability and genetic correlations with other psychiatric traits and disorders in European-ancestry subsets.

Results: We observed similar effects of civilian and military trauma across studies. No genome-wide significant hits were found in trans-ethnic GWAS including 5,000 cases. Interpolations from other PGC disorders suggest that we may be reaching the inflection point for first GWAS hits with 15,000 PTSD cases, results that will be presented. We found that PTSD liability was significantly influenced by genetics \((p<0.05)\), with SNP-based heritability being higher in women \((28\%, p<0.05)\) than in men \((7\%, NS)\). Polygenic methods showed a significant overlap of PTSD with other psychiatric disorders.

Conclusions: Very large sample sizes are needed to investigate the genetic architecture of PTSD. Our current findings show that PTSD is significantly influenced by genetic factors, which may vary between females and males, confirming findings from twin studies.

Supported By: R01MH108886

Keywords: PTSD - Posttraumatic Stress Disorder, Psychiatric Genomics Consortium, GWAS, Meta-analysis, Trauma

86. Epigenetic Signatures of PTSD: Results from the Psychiatric Genomics Consortium PTSD Epigenetics Workgroup

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Background: Post-traumatic stress disorder (PTSD) results from trauma, but not all individuals develop PTSD after trauma. Differences in susceptibility to PTSD may be related to epigenetic differences between cases and trauma-exposed controls that can provide insight into the biological processes underlying the disorder.

Methods: The PGC-PTSD Epigenetics Workgroup combined epigenome-wide data from a diverse group of nine military and civilian studies to conduct a cross-sectional meta-analysis of current PTSD in almost 1600 cases and trauma-exposed controls. For all samples, DNA methylation was measured in whole blood using the HumanMethylation450 BeadChip. EWAS was performed on each cohort followed by meta-analysis using inverse normal p-value combination and false discovery rate (FDR) estimation.

Results: Three CpG sites in the Aryl-hydrocarbon receptor repressor (AHRR) were associated with current PTSD \((FDR<.05)\), independent of age, sex, race, and cellular heterogeneity. Controlling for smoking attenuated some of these results. There were substantial differences in the results from military \((N=1,048)\) and civilian cohorts \((N=550)\), with analysis of military cohorts demonstrating association of the AHRR CpG sites \((FDR<.05)\) and civilian cohorts identifying association \((FDR<.05)\) of a CpG site in neuregulin 1 (NRG1), a gene previously implicated in schizophrenia and anxiety disorders.

Conclusions: The PTSD PGC EWAS meta-analysis has identified associations between PTSD and CpG sites in multiple biologically relevant genes. Future studies will: explicate the effect of trauma types across civilian and military cohorts; evaluate the association of identified CpG sites in longitudinal samples; and integrate GWAS data into ongoing EWAS analyses.

Supported By: R01MH106595

Keywords: Epigenome, DNA methylation, Trauma, Meta-analysis, Posttraumatic Stress Disorder

87. Volume of Sub-Cortical Structures in Posttraumatic Stress Disorder from Multi-Site Investigation by ENIGMA and PGC Consortia

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1Duke University Medical Center & Durham VA Medical Center, 2National Center for PTSD, 3Emory University, 4USC, 5Durham VA Medical Center, 6University of Western Ontario, 7University of Amsterdam, 8University of New South Wales, 9Harvard - McLean, 10University of Washington, 11University of Sydney, 12Utrecht UMC, 13Yale University, 14University of Michigan, 15VU University Medical Center, 16University of Cape Town

Background: Many studies report smaller hippocampal and amygdala volumes in PTSD, but findings are not always consistent. Here, we present the results of a large-scale neuroimaging consortium study on PTSD conducted by the PGC-ENIGMA PTSD Working Group.

Methods: We analyzed neuroimaging and clinical data from 1,888 subjects contributed by 16 cohorts, representing the largest neuroimaging study of PTSD. We assessed the volumes of nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, lateral ventricle, and total intracranial volume (ICV). We used a standardized
image-analysis and quality-control pipeline established by the ENIGMA consortium.

**Results:** The amygdala and hippocampus, after adjusting for age, sex, and ICV, were smaller in subjects with current PTSD (amygdala, $D = -0.11$, $p = 0.025$; hippocampus, $D = -0.17$, $p = 0.00054$). The ICV-unadjusted effect sizes for hippocampus and amygdala were larger (amygdala, $D = -0.16$, $p = 0.0058$; hippocampus, $D = -0.22$, $p = 0.000048$). Childhood trauma was associated with smaller amygdala volume ($D = -0.16$, $p = 0.0044$) and hippocampal volume ($D = -0.17$, $p = 0.0031$) in a model adjusting for age, sex, and ICV. The negative association with hippocampal volume in the female-only participants had a large effect size ($D = -0.31$, $p = 0.00012$). The other subcortical regions did not show significant PTSD or trauma effects. Whereas we hypothesized that both amygdala and hippocampus volume would differ in PTSD, the hippocampal result was significant after imposing a Bonferroni correction, which was not the case for the amygdala.

**Conclusions:** Our study represents an important milestone in an ongoing collaborative effort to examine the neurobiological underpinnings of PTSD and the brain’s response to trauma without the biases faced by meta-analyses of previously published data.

**Keywords:** PTSD - Posttraumatic Stress Disorder, Hippocampal Volume, amygdala volume, Childhood Trauma, subcortical volumes

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88. Identification of Psychophysiological Markers of PTSD Risk and Potential Use as Intermediate Phenotypes

Victoria Risbrough$^1$, Mark Geyer$^2$, Dean Acheson$^2$, Arpi Minassian$^2$, Adam Maihofer$^2$, Dewleen Baker$^1$, and Caroline Nievergelt$^2$

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**Background:** Psychophysiological markers offer a useful intermediate phenotype for genetic analysis of risk for complex psychiatric disorders because they are quantitative, objective, and can be interrogated in animal model systems. Here we examined if psychophysiological phenotypes consistently associated with posttraumatic stress disorder (PTSD), such as increased startle, cardiovascular function and conditioned fear learning, are also associated with risk for PTSD when assessed before trauma exposure and symptom development.

**Methods:** The Marine Resiliency Study is a prospective, longitudinal study of >4000 active duty Marines to identify biological, physiological and psychosocial markers of risk for PTSD. Participants were assessed with a 4-hr test-battery that included psychophysiological testing and PTSD symptom assessments both before a combat deployment and 3-6 months after returning.

**Results:** Low heart rate variability measured at predeployment was significantly associated with increased risk for PTSD after deployment ($OR = 1.47$, CI = $1.10$-$1.98$, $p = .001$) while high prepulse inhibition performance was associated with increased resiliency to develop PTSD after deployment ($OR = 0.32$, CI = $0.123$-$0.837$, $p = .005$). Those that went on to develop PTSD post-deployment also showed reduced safety-signal learning at pre-deployment compared to those that did not go on to develop PTSD ($p = .005$). Although altered startle reactivity and fear extinction were observed in subjects with PTSD ($p = .005$), these phenotypes were not associated with PTSD-risk before deployment.

**Conclusions:** These data indicate that specific physiological “intermediate” phenotypes are associated with PTSD risk, and support the hypothesis that these biological traits play a role in the etiology of PTSD. We will discuss opportunities and limitations of these phenotypes to the larger PGC-PTSD efforts.

**Supported By:** VA Merit Award, Center of Excellence for Stress and Mental Health, DOD

**Keywords:** PTSD - Posttraumatic Stress Disorder, Fear conditioning, Sensorimotor Gating, Startle response, Endophenotype

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89. Ace Background Influences Poor Sleep and Depression Cycle during Pregnancy

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$^1$Columbia University, $^2$Long Island University

**Background:** Dysregulation of mood and sleep are independent risk factors for adverse health outcomes, as are high levels of adverse childhood events (ACE). Pregnant adolescents are at increased risk for all three factors and therefore an enriched sample for beginning to differentiate the causal associations amongst these factors.

**Methods:** We followed a cohort of pregnant adolescents (ages 14-19, N = 185) throughout gestation, gathering abuse history and assessing pregnancy-related distress and sleep quality approximately once per trimester. We sought to: (1) clarify the directionality of associations between sleep and mood dysregulation using a cross-lagged auto-regressive path model, and (2) Examine variability in this association as a function of abuse history, using a multiple group analysis via the grouping command in Mplus.

**Results:** Across the sample, higher levels of sleep problems in the 2nd trimester were associated with increases in psychological distress by the 3rd ($\beta = .18$, $p = .036$). For the subsample who met criteria for abuse history, psychological distress in the 2nd trimester was associated with an increase in maternal sleep problems in the 3rd ($\beta = .25$, $p = .013$). Conversely, for women without an abuse history, higher levels of maternal sleep problems in the 2nd trimester were associated with an increase in maternal...
Conclusions: The interaction between psychological distress and sleep quality during pregnancy is not necessarily fixed. By using a woman’s personal history to inform her prenatal care, she can receive more targeted interventions.

Supported By: R01 NIMH

Keywords: ACE, trauma, sleep, depression, pregnancy

90. Second Generation Effects of Trauma: Evidence for Developmental Programming

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1Mount Sinai School of Medicine/JJP VA, 2James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, 3Mount Sinai School of Medicine, 4Harvard University, 5Max-Planck Institute of Psychiatry

Background: Developmental programming is known to mediate some effects of trauma exposure in childhood, and may be critical to the appearance of intergenerational trauma effects. The data shown will support the idea that effects of a preconception trauma on offspring functional and molecular biology may differ based on parental gender and age at the time of exposure.

Methods: Two studies were conducted in Holocaust offspring and Jewish controls. In the first, 24-hr urinary cortisol and 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) activity were determined using GCMS; for the second, lymphocyte FKBP5 methylation was assessed by pyrosequencing.

Results: Reduced cortisol excretion ($\beta = .046$) and elevated 11β-HSD-2 activity ($\beta = .008$) were observed in offspring compared to controls, particularly among those whose mothers had been children during World War II ($\beta = .029$). In the second study, FKBP5 methylation at intron 7, site 6 was higher among females than males ($F(1,93) = 14.76$, $p < .0005$), and lower in Holocaust offspring than controls ($F(1,93) = 4.655$, $p = .034$, controlling for gender). There was a significant effect of age of maternal exposure ($F(3,70) = 5.776$, $p = .001$, controlling for gender and age of paternal exposure) that was based on reduced methylation in offspring with maternal exposure in childhood ($p = .005$). There were no significant associations of FKBP5 methylation with age of paternal exposure.

Conclusions: These data demonstrate specific associations between preconception parental trauma and offspring neuroendocrine and molecular glucocorticoid regulation, and point to childhood maternal exposure as a critical determinant of intergenerational transmission. The results complement observations from previous work and are consistent with the influence of glucocorticoid programming.

Supported By: NIMH (1RC1MH088101-01) “Identification of an Epigenetic Risk Marker for PTSD”; NIMH (R01 MH 64675-01) “Biology of Risk and PTSD in Holocaust Survivor Offspring”

Keywords: intergenerational, Trauma Exposure, developmental programming, DNA methylation, FKBP5

91. Maternal Early Life Adversity: Impact on Offspring Stress Responsiveness

Cynthia Epperson, Kathleen Morrison, Liisa V. Hantsoo, Grace Ewing, Jessica Podcasy, Mary D. Sammel, and Tracy L. Bale

University of Pennsylvania

Background: One mechanism by which maternal childhood adversity may impact offspring development is through programming of the maternal and infant hypothalamic pituitary adrenal axis (HPA-A)

Methods: Maternal psychophysiologic response to a mild stressor was assessed twice during pregnancy (n = 90) and once at 6 weeks postpartum. One-third of women reported experiencing at least two adverse childhood experiences before the age of 18 and were considered the High ACE Group, while those with zero or one ACE formed the Low ACE Group. Finally mother-infant pairs underwent a separation stressor and the infants a restraint and noise stressor at 6 months of age. Salivary cortisol was collected across each procedure from both mothers and infants according to previously published methods. Cortisol levels were log transformed and repeated measures mixed-model ANOVA was performed to evaluate ACE category and time as predictors of cortisol change-from-baseline, controlling for race as a confounder.

Results: ACE category predicted log-transformed cortisol change-from-baseline ($F < .05$), with High ACE women, on average, experiencing a 50% lower cortisol response to the infant separation paradigm than did low ACE women. Infants of High ACE mothers also demonstrated lower cortisol response to restraint and noise stress (with no difference by sex). Maternal stress response during pregnancy will be discussed in relationship to infant response postpartum.

Conclusions: Maternal early life stress contributes to altered cortisol response to an ecologically relevant postpartum stressor, namely separation from the offspring, that is then mirrored in the offspring during their stress exposure. To date, findings are similar in male and female infants.

Supported By: R01 MH0999110

Keywords: Early Life Stress, Pregnancy, offspring, HPA Function, prenatal maternal stress

92. Sex Differences in Resting State Functional Connectivity (rs-FC) of Limbic Circuits in PTSD

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1Columbia University Medical Center, 2NYSPI and Columbia University, 3Columbia University

Background: Women are at twofold risk of posttraumatic stress disorder (PTSD) following trauma than men. Studies of sex differences have been mostly epidemiological, few examining neural mechanisms despite literature identifying
neural substrates of PTSD. Neural dysregulation in PTSD includes hippocampus (HIP), basolateral amygdala (BLA), and medial prefrontal cortex (mPFC), key hubs of the limbic system. Animal studies show sex-specific effects of stress on plasticity in this circuit, with dendritic branching from mPFC to BLA increased among females and retracted among males. Little data exists on sex differences in connectivity within this circuit in humans.

**Methods:** We examined resting state functional connectivity (rs-FC) of BLA and HIP to mPFC regions among trauma-exposed men (N = 30; 19 PTSD) and women (N = 54; 31 PTSD). Female vs. male contrasts were tested within predefined targeted ROIs (mPFC), with BLA and HIP as seeds, in the entire group and within PTSD/non-PTSD groups. We hypothesized higher rs-FC between mPFC and BLA among women than men. We explored mPFC-HIP connectivity and PTSD-related sex differences.

**Results:** Both BLA and HIP had higher rs-FC to mPFC for women than men in the overall sample (all pFWE-corr < .05). This pattern appeared in the PTSD, but not non-PTSD, group. **Conclusions:** Our hypothesis was supported, with findings mirroring animal studies. We uncovered sex-related differences in mPFC-HIP connectivity. Sex differences were specific to PTSD. A possible mechanistic explanation is estrogen-related neural plasticity during stress, evident in mPFC and HIP and tied to mPFC dendritic branching to BLA. Multimodal, within-group analyses for men and women are needed to further elucidate mechanisms.

**Supported By:** This data was collected as part of a project supported by grants R01MH072833 and R01MH105355 from the National Institute of Mental Health (Dr. Neria, Principal Investigator), and the New York State Psychiatric Institute. Dr. Helpman's work is supported by grant T32 MH096724 from the National Institute of Mental Health (Wainberg, Oquendo Principal Investigators).

**Keywords:** Neural Networks, Women, Sex-specific, Trauma Exposure, PTSD

**SYMPOSIUM**

**Subtype-Specific NMDA Receptor Pathology: Beyond (genetic) Hypofunction in Schizophrenia**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM

Sapphire 400 AB

Chair: Bernat Kocsis

Co-Chair: Tomas Guilarte

93. NMDAR-reactive Lupus Autoantibodies Alter Spatial Memory, Place Cell Function and Dendritic Architecture of Hippocampal Neurons

Patricio Huerta

Northwell Health

**Background:** Neuropsychiatric systemic lupus erythematosus (NPSLE) refers to the neurologic manifestations of SLE, which develop insidiously and cause impaired cognition and executive function. Most NPSLE patients carry antibodies (termed DNRAbs) that bind DNA and the GluN2A and GluN2B subunits of the NMDAR. Mechanistic studies show that DNRAbs bind the NMDAR and augment NMDAR-mediated responses. When DNRAbs are injected into mouse hippocampus, they can cause apoptosis of pyramidal neurons (~10–20% of cells), together with poorly-understood network dysfunction that we have examined in our studies.

**Methods:** We use a transdisciplinary approach which includes studies in SLE patients, as well as murine SLE models, in which we apply behavioral assessments, in vivo electrophysiology, ex vivo slice studies (synaptic recordings, optical imaging), and structural analysis (2P confocal microscopy, Golgi stain).

**Results:** DNRAb+ lupus patients (n = 45) display a selective impairment in spatial recall when compared to control subjects (n = 30). In a mouse model of SLE, when circulating DNRAbs penetrate the hippocampus, they cause impaired memory flexibility. Neural recordings in DNRAb+ mice (n = 15) reveal that CA1 place cells exhibit a significant expansion in place field size. Structural analysis shows that hippocampal pyramidal cells have substantial reductions in their dendritic processes and spines. Strikingly, these abnormalities become evident at a time when DNRAbs are no longer detectable in the hippocampus.

**Conclusions:** Our results indicate that DNRAbs cause selective impairment of spatial memory in patients and mice. Mouse studies reveal structural and functional deficiencies in CA1 place cells that might represent the neural correlate of the spatial impairment.

**Supported By:** NIH Program projects 5P01-AI073693-08 and 5P01-A102862-03

**Keywords:** brain autoimmunity, NMDA Receptor, Spatial Navigation, Hippocampus

94. Early Life Lead Exposure and Schizophrenia: An Environmental Model of NMDA Receptor Hypofunction

Tomas Guilarte

Florida International University

**Background:** Environmental factors have been associated with psychiatric disorders and recent studies suggest an association between prenatal lead exposure and schizophrenia. Early life lead exposure (ELLE) in a rodent model recapitulates key cognitive and neuropathological findings present in schizophrenia subjects. Lead is a potent NMDA receptor (NMDAR) antagonist and exposure in early life alters the ontogeny of NMDAR subunits leading to deficits in synaptic plasticity and cognitive function. Specifically, ELLE arrests the ontogenetic switch of NMDAR subunits from a predominantly NR2B-containing complex in early life to a NR2A subunit NMDAR complex in the adult brain.

**Methods:** We used behavioral, electrophysiological, and molecular methods in a rodent model of Pb exposure to further investigate this link.

**Results:** Thus, lead-exposed adult animals exhibit a decreased proportion of the total NMDAR current that is NR2A subunit dependent relative to controls. This finding is relevant to hallmark pathology in schizophrenia since...
NR2A-NMDAR complexes are important for the maintenance of parvalbumin (PV) and glutamate decarboxylase (GAD67) positive GABAergic interneurons, the same neurons that are decreased in the schizophrenia brain and in the brain of lead exposed animals. One functional consequence of the loss of PV+ GABAergic interneurons is hyperactivity of the dopaminergic system, a hallmark feature of schizophrenia. Lead exposed animals exhibit a significantly higher response to cocaine and have higher levels of striatal dopamine metabolites consistent with a hyperactive subcortical dopaminergic system.

**Conclusions:** Collectively, these findings provide strong evidence that ELLE may be a risk factor for mental disorders.

**Supported By:** NIEHS grant number ES006189

**Keywords:** Schizophrenia, Lead, NMDA Receptor, GABA, Dopaminergic signalling

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**95. Role of NR2A-Containing Receptors in Early Stage of Migraine**

Minyan Wang

Xi’an Jiaotong-Liverpool University

**Background:** NMDA receptor (NMDAR) antagonists are known to be the most effective drugs to suppress cortical spreading depression (CSD), the underlying cause of migraine aura, which may also lead to migraine headache through Pannexin1 (Panx1) channels activation. However, these antagonists are still perceived as unlikely candidate for migraine treatment because of their unacceptable side effects. The aim of this study was to explore the role of NR2A-containing NMDA receptors in migraine pathophysiology and its molecular mechanism.

**Methods:** Multidisciplinary approaches including electrophysiology, intrinsic optical imaging, western blot, immunohistochemistry were applied.

**Results:** The data firstly demonstrated that NMDAR antagonists, with major type NR2 subunit selectivity, suppressed CSD in vitro. Using electrophysiology, the role of NR2A in mediating CSD genesis and propagation was further confirmed in rats. Further molecular mechanism of migraine study showed that NR2A inhibition by NVP-AAM077, injected through intracerebral ventricle not only suppressed CSD-induced elevation of Src phosphorylation, but also inhibited CSD induced increase in interaction between Panx1 and Src and the Panx1 channel opening in ipsilateral cortex of rats. Similarly, the elevated Src activation and Panx1 opening induced by CSD was also markedly prevented by the Src family kinases (SFK) inhibitor, PP2 in addition to its prevention of cortex susceptibility to CSD.

**Conclusions:** This study reveals a previously unknown NR2A-Src-Panx1 pathway in migraine pathophysiology, suggesting therapeutic benefit of NR2A-preferring antagonist for preventing migraine with alleviated side effect.

**Supported By:** XJTLU and Wangwenli Charitable foundation

**Keywords:** NR2A, Migraine, Cortical spreading depression, Src family kinase, PANX1

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**96. Subunit-Specific NMDR Blockade Produce Distinct Effects on Mesoscale Brain Dynamics**

Benjamin Pittman-Polletta, Kun Hu, and Bernat Kocsis

Harvard Medical School

**Background:** Narrowband high-frequency oscillations (HFOs, ~140Hz) are a recently discovered form of rhythmic activity potentiated by ketamine. They are most likely generated by mesolimbic networks which receive inputs from hippocampus and frontal cortex. HFOs are commonly observed coupled to low-frequency oscillations (<10Hz) which might originate from these inputs. However, while theta rhythm (~8Hz) is associated with hippocampal circuitry, prefrontal cortex activity is organized by delta-range (4Hz) oscillations. This study examined the effects of subtype-specific NMDA-R antagonism on low-frequency modulation of HFO amplitude to probe the altered system of coupling between these networks.

**Methods:** Spectral analyses and phase-amplitude coupling (PAC) were performed on local field potentials in frontal and occipital cortex and hippocampus after administration of NR2A-preferring antagonist NVP-AAM077 and the non-specific NMDA-R antagonist MK-801.

**Results:** Following MK-801 injection, comodulograms revealed dramatic increases in theta-HFO PAC in all brain regions relative to saline injection whereas following NVP-AAM077 injection, the largest observed effect was a delayed increase in delta-HFO PAC at all sites, relative to saline. As revealed by spectral analyses, delta vs. theta modulation of HFO corresponded to the relative dominance of frontal delta power to hippocampal theta power.

**Conclusions:** These results suggest that low-frequency modulation of HFO amplitude may be an indicator of cortical vs. hippocampal control of mesolimbic circuits. Since HFO activity predominantly reflects mesolimbic population activity, its phase modulation may reflect the strength of inputs, their balance, to the mesolimbic system. As shown here, subtype-specific NMDAR blockade produce distinct effects on this balance which might lead to subtype-specific deficits related to schizophrenia.

**Supported By:** NIH R01 MH100820, ES006189

**Keywords:** Slow wave oscillations, Cross-frequency coupling, Hippocampus, Fronto-limbic Connectivity

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**SYMPOSIUM**

**Cerebral Cortex and Genetic Vulnerability in Impulsive-Compulsive Spectrum Disorders**

Thursday, May 18, 2017, 3:00PM - 5:00PM

Sapphire 410 AB

Chair: Odile van den Heuvel

Co-Chair: Paul Thompson
97. Neuroimaging of Cortical Brain Alterations in Adult and Pediatric Obsessive-Compulsive disorder: Preliminary Findings from the ENIGMA Obsessive-Compulsive Disorder Working Group

Premika Boedhoe1, Lianne Schmaal2, Paul M. Thompson3, Dan J. Stein2, Odile A. van den Heuvel1, and ENIGMA-OCD Working Group5

1VU University Medical Center, 2Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia, 3Imaging Genetics Center, Department of Neurology, Keck School of Medicine, University of Southern California, 4University of Cape Town, South Africa, 5International Collaboration

Background: Structural MRI studies on OCD have been numerous, but not always consistent. To address this issue, we initiated the ENIGMA-OCD working group. Here, we present results of the largest study to date on cortical brain measures in both adult and pediatric OCD patients and healthy controls using an individual participant data (IPD) meta-analysis approach.

Methods: Structural T1-weighted MRI scans including 1905 OCD patients and 1760 healthy controls from 27 research sites worldwide were processed locally using FreeSurfer. Cortical thickness and surface area measures were analyzed separately for pediatric (17y and younger) and adult (18y and older) subjects using regression models controlling for age and gender, and combined in random-effect meta-analysis models. Results were considered significant if the P-value exceeded a significance threshold determined by the false discovery rate (FDR) procedure at q = 0.05.

Results: We found significantly lower surface area in the transverse temporal gyrus (effect size d: -0.16) in adult OCD patients compared to controls. In medicated adult OCD patients, we found significantly thinner cortices of frontal and temporal areas (effect size d between -0.15 and -0.29). In medicated pediatric OCD patients compared to controls significantly lower surface area was observed of frontal, temporal, parietal and cingulate regions (effect size d between -0.28 and -0.49).

Conclusions: Our study suggests that cortical thickness and surface area measures may be differentially affected by OCD at different stages of life and moderated by medication status. Our next step is to perform a mega-analysis to understand how these medication effects are related to disease severity and comorbidities.

Supported By: 1. NIH: BD2k (Big Data), U54 EB020403-02 (PI: Thompson) 2. Neuroscience Campus Amsterdam (NCA), IPB-grant (PI’s: Schmaal / van den Heuvel)

Keywords: Obsessive Compulsive Disorder (OCD), Cortical Thickness, Cortical surface area, structural neuroimaging

99. A Large Scale Study of Cortical and Cerebellar Morphology in ADHD across the Life span: An ENIGMA-ADHD Collaboration

Philip Shaw1, M Hoogman2, J Bratlen2, M Onnink2, E Shumskaya2, M Mennes2, M Zwiers2, D Hilbar3, ENIGMA ADHD Working Group3, P Thompson3, and B Franke4

1NIMH, 2Radboud University Medical Center, 3Imaging Genetics Center, University of Southern California, 4ENIGMA-ADHD

Background: Many studies have reported structural brain differences between alcohol dependent and non-dependent individuals, but conclusions are limited due to the heterogeneity across methods used to process and parcelle structural data, and confirm alcohol dependent status. This study aims to pool results from existing addiction-neuroimaging studies using ENIGMA protocols for harmonising neuroimaging data and ENIGMA-Addiction procedures for harmonising addiction phenotypes.

Methods: A bibliographic review identified neuroimaging studies of substance-dependent individuals and matched controls. Authors were contacted and invited to contribute their data to the consortium by a specified date. ENIGMA protocols were used to re-process neuroimaging data and parcelle subcortical and cortical brain regions using FreeSurfer. Consensus on methods for harmonising addiction phenotype was reached following a review of all study protocols and databases. This analysis includes 8 studies that confirmed alcohol dependent status using DSM-IV diagnostic criteria. ENIGMA protocols were used to conduct meta-analysis on each region using covariates specified by other ENIGMA working groups to maximise potential comparisons across disorders.

Results: Meta-analyses pooling effect sizes (ES) across studies indicated moderate ESs across a number of subcortical and cortical regions. Regions for which ES yielded confidence intervals that did not cross zero were: anterior and posterior cingulate, fusiform, inferior temporal gyrus and temporal pole, cingulate gyrus, lateral and medial orbital frontal cortex, insula and all subcortical regions.

Conclusions: Effect sizes are presented as they compare to ESs yielded from meta-analyses comparing major depression or schizophrenia cases to matched controls and indicate widespread and significant brain impairment in alcohol dependence.

Supported By: Consortium grant (U54 1150 EB 020403) from the NIH Institutes contributing to the Big Data to 1151 Knowledge (BD2K) Initiative

Keywords: Addiction, Neuroimaging, Meta-analysis

98. Cortical and Subcortical Differences between Alcohol Dependent Individuals and Controls: Meta Analysis Results from the Enigma-Addiction Working Group

Patricia Conrod1, Hugh Garavan2, Scott Mackey2, Jacob Lavoie2, David Glahn2, and Enigma Addiction Working Group3

1University of Montreal, 2University of Vermont, 3Yale University, multiple
working group now aims to study cortical and cerebellar measures across the life-span.

**Methods:** Thirty-four sites currently participate (2197 cases, 1926 controls). All sites have used automated, validated segmentation softwares (FreeSurfer to measure thickness and surface area of 34 cortical regions; MAGEt to measure 21 cerebellar regional volumes). Meta- and mega-regressions have combined site-specific case-control differences. Developmental trajectories were modelled through age stratification, fractured polynomials (cortex) and piecweise linear mixed model regression (cerebellum). Effects of medication, symptom severity and comorbidity are considered.

**Results:** Subtle but significant reductions in cortical thickness localized to temporal (temporal pole, fusiform gyrus, entorhinal cortex) and frontal regions (pre/paracentral gyrus). The largest effect size was for total surface area: $d = -0.21$. Differences were larger in children than adults. Cerebellar analyses found significant baseline volume reductions in ADHD (effect sizes around 0.2). Trajectory analyses showed that diagnosis differed in its impact on the growth of cerebellar grey and white matter.

**Conclusions:** We find reduced fronto-temporal cortical and cerebellar regions in ADHD. The most compromised cortical regions—fusiform gyrus and temporal pole—are connected to the amygdala, which showed the largest case-control difference in our subcortical study, highlighting the role of emotional processing in ADHD. Cortical age analyses show delayed maturation and lower peak volumes in ADHD. Preliminary cerebellar analyses also find baseline reductions in ADHD, along with altered developmental trajectories.

**Supported By:** Intramural Program of the NHGRI

**Keywords:** Attention Deficit Hyperactivity Disorder, Brain Imaging, Meta-analysis, Brain cortex, Cerebellum

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100. Investigating the Overlap between Common Genetic Factors for ADHD Risk and Brain Volume Measures

Marieke Klein$^1$, Jason L. Stein$^2$, ENIGMA$^2$, consortium chaired by Paul Thompson$^3$, ADHD Working Group of the Psychiatric Genomics Consortium represented by Steve Faraone$^4$, Anders Borglum$^5$, Stephen V. Faraone$^6$, Paul M. Thompson$^7$, Sarah E. Medland$^6$, Alejandro Arias-Vasquez$^7$, and Barbara Franke$^7$

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**Background:** Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that has a complex genetic background. Several brain structures differ in size between people with ADHD and healthy individuals. Since both ADHD risk and brain volumes are highly heritable, we hypothesized that both traits are genetically linked by shared common variant architecture.

**Methods:** We integrated genome-wide association results from the largest publicly available studies of ADHD (N = 55,374; PGC+IPSICH ADHD working groups) and regional brain volumes (N = 11,772; ENIGMA consortium). To investigate overlap between common genetic variation associated with ADHD risk and brain volume measures (intracranial volume (ICV), accumens, amygdala, caudate, hippocampus, and putamen), we used a set of complementary methods, extending a recent analysis of schizophrenia.

**Results:** Meta-analysis of single variants revealed significant loci of interest associated with both ADHD risk and ICV volume. Overall, genetic correlations between ADHD risk and the different brain volumes were low. SNP effect concordance analysis showed significant concordance of allelic effects between ADHD risk variants and variants associated with smaller ICV ($P = 0.0009$). Strongest pleiotropy was seen for putamen ($P = 0.0089$) and revealed one variant significantly influencing both ADHD risk and putamen volume (rs6508207, PADCAD = 7.76E-06, Pputamen = 0.00013). Conjunction analysis supported the locus of rs6508207 at sub-threshold level.

**Conclusions:** This first genome-wide study of genetic overlap between brain volume measures and ADHD revealed genetic covariation on the single variant level, but limited covariation on a global level. These findings can help us to develop new hypotheses about biological mechanisms, by which brain structure alterations may be involved in ADHD disease etiology.

**Supported By:** Grants were received from Netherlands Organization for Scientific Research (NWO Brain & Cognition Excellence Program (433-09-229), Vici grant to B.F. (016-130-669), Netherlands Brain Foundation (grant 15F07227), BBMRI-NL (CP2010-33), and European Community’s Seventh Framework Programme (FP7/2007–2013; 602805).

**Keywords:** ADHD, MRI brain imaging, Genetics

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**SYMPOSIUM**

**Network Medicine: Target Identification and Engagement**

Thursday, May 18, 2017, 3:00 PM - 5:00 PM
Aqua AB

**Chair:** Noah Philip

101. Network Mechanisms of Clinical Response to Transcranial Magnetic Stimulation in Posttraumatic Stress and Major Depressive Disorders

Noah Philip$^1$, Jennifer Barredo$^2$, Mascha v ‘ant Wout$^3$, Jorge Almeida$^4$, Audrey Tyrka$^5$, Lawrence Price$^6$, and Linda Carpenter$^6$

$^1$Dept of Psychiatry and Human Behavior, Alpert Medical School of Brown University/Center for Neurorestoration and Neurotechnology, Providence VA, $^2$Providence VA Medical Center, $^3$Brown/Providence VA Medical Center, $^4$Dept of Psychiatry and Human Behavior, Alpert Medical
School of Brown University, ‡Butler Hospital - Brown Medical School, §Brown University, Butler Hospital

**Background:** Treatment with repetitive transcranial magnetic stimulation (TMS) can modulate pathological functional connectivity in patients with major depressive disorder (MDD). Posttraumatic stress disorder (PTSD) is often comorbid with MDD, and TMS can alleviate symptoms of PTSD. This is the first study to evaluate TMS-associated changes in connectivity, in patients with comorbid PTSD and MDD.

**Methods:** Resting state functional connectivity was acquired on 33 participants, before and after 5Hz TMS therapy to left dorsolateral prefrontal cortex (DLPFC). Analyses used a priori seeds relevant to TMS, MDD or PTSD: the subgenual anterior cingulate cortex (sgACC), DLPFC, hippocampus, and basolateral amygdala, to compare pre- vs. post-treatment RSFC associated with clinical changes, adjusting for age and baseline symptom severity. Results were corrected using cluster-based FDR, plus leave-one-out cross-validation. Connectivity changes were further explored using data-driven multivoxel pattern activation (MVPA).

**Results:** After TMS there was reduced RSFC between the sgACC and default mode regions, DLPFC, and insula (corrected p < .001), alongside reduced connectivity between the hippocampus and the dorsal anterior cingulate cortex (dACC), and putamen (corrected p < .001). MVPA indicated changes in connectivity of the hippocampus, amygdala, dACC, caudate and fusiform (corrected p < .001). Anticorrelations between the sgACC and DMN predicted response, as did amygdala to ventromedial prefrontal cortex connectivity (corrected p < .001).

**Conclusions:** These results are consistent with prior work that implicate reduced default network with TMS in MDD, and demonstrates that TMS can uncouple hippocampal connectivity from PTSD-relevant regions of the salience network. Furthermore, this work indicates there may be network-based biomarkers of response that are relevant to commonly comorbid disorders.

**Supported By:** US Dept of Veterans Affairs, IK2 CX000724; Investigator-initiated grant from Neuronetics

**Keywords:** Repetitive Transcranial Magnetic Stimulation, PTSD - Posttraumatic Stress Disorder, Major Depressive Disorder (MDD), Connectivity

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**102. Modulating Top-Down Executive Control Networks with Striatal Deep Brain Stimulation**

Alik Widge¹, Samuel Zorowitz¹, Matthew Boggess¹, Earl Miller², Thilo Deckerbach¹, and Darin Dougherty¹

¹Massachusetts General Hospital, ²Massachusetts Institute of Technology

**Background:** Deep brain stimulation (DBS) of the ventral internal capsule/ventral striatum (VC/VS) is a promising treatment for major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). Clinical trial results are mixed, in part because the mechanism of action remains unknown. VC projects throughout prefrontal (PFC) and cingulate cortices, and we hypothesized that DBS might act through these fibers to enhance the function of fronto-cingulate networks involved in top-down control.

**Methods:** 12 patients with VC/VS for either OCD or MDD performed the Multi-Source Interference Task (MSIT) with DBS on, then again after 1 hour off DBS. MSIT robustly engaged our target network. We recorded 64-channel EEG (n = 8 usable) and projected scalp activity to the cortex using MNE-Python and a patient-specific head model. We assessed evoked EEG with a sliding multivariate regression, using temporal cluster correction and FDR adjustment at the label level.

**Results:** DBS improved reaction times (RT) by an average of 34 ms (p < 1.8e-52, t-test on GLM coefficient). It did not modulate evoked potentials, but increased evoked theta (5-8 Hz) power in the dorsal and ventro-lateral (VL) PFC and posterior cingulate (all clusters FDR-corrected p < 0.05). The strongest DBS effect in VLPCF matched the window when RT was strongly encoded in theta power.

**Conclusions:** VC/VS DBS improves patients’ performance on a top-down control task. This improvement is correlated with increases in EEG oscillations believed to implement top-down control, in a network of cortical labels linked to that function. The results are consistent with an effect of DBS on frontal executive networks.

**Supported By:** DARPA SUBNETS

**Keywords:** Deep Brain Stimulation, EEG, Prefrontal Cortex, Cingulate cortex

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**103. Increased Default Mode Network (DMN) Connectivity with Attention Networks with a Mindfulness-Based Intervention for PTSD: Seed and Whole Brain Connectomics Analyses**

Anthony King, Mike Angstadt, Chandra Sripada, and Israel Liberzon

University of Michigan

**Background:** Posttraumatic stress disorder (PTSD) affects ~10% general population and ~20% of combat veterans. Trauma-focused exposure treatments have very high efficacy in RCTs, but also high drop-out. PTSD shows altered within-network functional connectivity (FC) in salience network (SN) and default mode network (DMN), and increased DMN-SN cross-network FC. Mindfulness training is associated with improvement in rumination, depression, and PTSD, and increased DMN connectivity to attention networks.

**Methods:** In a pilot RCT of Mindfulness-Based Exposure Therapy (MBET), OEF/OIF veteran PTSD patients (N = 31) were assigned to MBET or comparison intervention (PCGT), Pre- and post-therapy fMRI (3Tesla) examined seed-based (DMN: PCC, vmPFC, SN: amygdala, insula) FC and whole-brain connectomics during standard “resting state”, and during in-scanner mindfulness “task”. Whole-brain connectomics calculated pair-wise Pearson correlations of time-series from 1068 ROIs, decomposed into spatial components using joint Independent Components Analysis (ICA). Effects of mindfulness task at intake, and longitudinal pre-post effects were tested (group x time interaction).
Results: At intake, seed-based analyses found PTSD Avoidant symptoms negatively correlated with DMN-DLPFC FC, and self-report rumination positively correlated with DMN-insula FC. Whole-brain connectomics found increased FC between DMN and dorsal attention network (DAN) during the mindfulness task. MBET was well-tolerated, had better patient retention than PCGT (p<.005), and significantly improved PTSD (p<.006, pre-post Cohen’s d = .85). In pre-post groupXtime analyses, MBET (but not PCGT) increased FC between DMN and attention networks (DLPFC, dACC), related to improvement in avoidant symptoms.

Conclusions: Brain connectivity network analyses suggest changes in DMN FC with attention networks underlie PTSD symptom improvement, suggesting a novel therapeutic mechanism.

Supported By: DOD TATRC W81XWH-08-2-0208; Mind and Life Institute

Keywords: PTSD - Posttraumatic Stress Disorder, Brain networks, Functional connectivity, Mindfulness, Avoidance

104. Cortical Oscillations: Target Identification, Engagement, and Validation

Flavio Frohlich
UNC - Chapel Hill

Background: We propose that restoration of cortical oscillations with transcranial alternating current stimulation (tACS) represents a promising new treatment approach. We focus on synergistic integration of computer simulations, animal model systems, and human studies to elucidate how tACS alters cortical oscillations to enable the rational design of novel tACS interventions for psychiatric illness.

Methods: We built a biophysical model of the thalamo-cortical system. We applied tACS to head-fixed awake ferrets (N = 2) and recorded interaction dynamics between the pulvinar and posterior parietal cortex by simultaneous extracellular recordings. In humans, we combined hdEEG with tACS to establish the presence of outlasting effects of tACS on alpha oscillations as a function of state, assessed by pupil diameter and heart rate variability (N = 20). We further performed a clinical trial of tACS for the treatment of major depressive disorder, combined with assessment of target engagement by hdEEG (N = 30).

Results: Together, our investigation of target engagement and validation of tACS for the modulation of alpha oscillations have revealed that tACS successfully enhances alpha oscillations by means of resonance. The effects of tACS are gated by behavioral states and are mediated by modulation of cortical activity, which is reflected in the activity of thalamic networks. Unblinded results of the clinical study will be presented.

Conclusions: Our results demonstrate that alpha oscillations are susceptible to tACS and that the effect of tACS is modulated by state. Refinement of stimulation paradigms based on this emerging mechanistic underpinning of tACS will accelerate the development of novel treatments that target pathological changes in cortical oscillations.

Supported By: NIMH R01MH11889 NARSAD

Keywords: Brain Stimulation, noninvasive brain stimulation, tACS, theta and alpha oscillations

105. Human BNST is Selective to Uncertain Threat and Modulated by Anxiety

Jennifer Blackford, Jacqueline Clauss, and Suzanne Avery
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Background: Rodent studies demonstrate that the BNST mediates sustained anxiety-like responses to uncertain threat, in contrast to the amygdala which mediates fear-like responses to immediate threats. While these data suggest an important role, the BNST has been remarkably understudied in humans. We recently overcame the technological issues that limited neuroimaging of the human BNST (Avery, 2014). Here we report on a translational task designed to directly compare BNST and amygdala function in humans.

Methods: Forty-five young adults completed a cued face anticipation fMRI task with three conditions: uncertain threat; certain threat; and certain safe. An ANOVA tested for an interaction of region (BNST vs amygdala) and condition. Whole brain and BNST connectivity analyses were performed and effects of social anxiety were investigated.

Results: Direct comparison of the BNST and amygdala revealed unique responses to threat: BNST activity was elicited by uncertain threat cues (brain region x cue interaction, p < .05), whereas amygdala activity was heightened in response to face images. During unpredictable threat, BNST-caudate connectivity was heightened and BNST-temporal pole connectivity was decreased. Social anxiety predicted heightened BNST reactivity to threat images (relative to neutral images) that followed the uncertain threat cues (p < .05) and correlated with BNST-hippocampal connectivity (r = -.33, p = .03).

Conclusions: Here, we show that the BNST responds to uncertain threat cues in humans. We also find for the first time, an effect of social anxiety on BNST reactivity and connectivity, providing evidence for a role of the BNST in social anxiety.

Supported By: VA Merit; NIMH R21; NIMH K01

Keywords: Anxiety, social anxiety, BNST, Amygdala

106. The Role of Oxytocin Neurons in the Bed Nucleus of the Stria Terminalis in Mediating Social Withdrawal

Natalia Duque-Wilckens1, Michael Steinman1, Valery Grinevich2, and Brian Trainor3

Keywords: Brain Stimulation, noninvasive brain stimulation, tACS, theta and alpha oscillations

Supported By: VA Merit; NIMH R21; NIMH K01
1University of California Davis, 2Department of Molecular Neurobiology, Max Planck Institute for Medical Research, Heidelberg, Germany, 3Department of Psychology, University of California Davis

**Background:** An evolutionarily conserved group of oxytocin (OT) cell bodies in the bed nucleus of the stria terminalis (BNST) was recently found to be affected by social defeat stress in females but not males. Here we conducted experiments to test the hypothesis that hyperactivity of OT neurons in BNST contributes to social withdrawal in females.

**Methods:** We used vivo morpholinos to knock down OT in the BNST in order to determine the behavioral effects of this specific population of OT neurons in control and stressed female California mice (Peromyscus californicus). We also used an OT promoter driven AAV expressing Venus to identify putative projections of BNST OT neurons. Finally, V1a receptor (V1aR) and oxytocin receptor (OTR) antagonists were used to determine which receptors mediate the effects of OT on behavior.

**Results:** Morpholino OT antisense reduced expression of OT neurons, and there was a significant negative correlation between the number of OT neurons in BNST and social interaction in stressed females but not control females. Venus positive fibers originating from BNST OT neurons were detected in the nucleus accumbens (NAc), but V1aR antagonist infused in the NAc had no effect on social interaction in stressed females. However, a single acute treatment of systemic OTR antagonist treatment increased social interaction in stressed females. To achieve this same effect with selective serotonin reuptake inhibitors, four weeks of treatment is required.

**Conclusions:** These results suggest that hyperactivity of BNST oxytocin neurons may contribute to stress-induced behavioral pathology and that OTR antagonists may have unappreciated therapeutic value.

**Supported By:** NIH R01 MH103322

**Keywords:** Bed nucleus of the stria terminalis, Oxytocin, social defeat stress, Anxiety, Depression

### 107. BNST Cell Type-Selective Changes in Gene Expression in Response to Chronic Stress

Donald Rainnie1, Sarah Daniel0, Aurelie Menigoz2, JiDong Guo2, Steven Ryan3, and Shivani Seth2

1Emory University School of Medicine Department of Psychiatry, 2Emory University School of Medicine

**Background:** Distinct regions and cell types in the bed nucleus of the stria terminalis (BNST) act to modulate anxiety in opposing ways. A history of chronic stress increases anxiety-like behavior and has lasting electrophysiological effects on the neurons in the BNST. However, the opposing circuits within the BNST suggest that stress may have differential effects on the individual cell types that comprise these circuits in order to shift the balance of the circuit to favor anxiogenesis. Yet the effects of stress are generally examined by treating all neurons within a particular region of the BNST as a homologous population.

**Methods:** We used patch-clamp electrophysiology and single cell quantitative reverse transcriptase polymerase chain reaction (scRT-PCR) to determine how chronic shock stress (CSS) affects electrophysiological and neurochemical properties of Type I, Type II, and Type III neurons in the BNSTALG.

**Results:** CSS resulted in changes in the input resistance, action potential waveform, and firing rate of Type III but not Type I or II neurons. Additionally, only the Type III neurons exhibited an increase in CRF mRNA and decrease in STEP mRNA expression after CSS. In contrast, only non-Type III cells showed a reduction in calcium permeable AMPA receptor (CP-AMPAR) current and changes in mRNA expression of genes encoding AMPA receptor subunits after CSS.

**Conclusions:** Type III neurons play a unique role in the BNST circuit and represent a population of CRF neurons particularly sensitive to chronic stress. Selective targeting of CRF neurons offers a novel avenue into the treatment of stress-related moods disorders.

**Supported By:** NIMH R01

**Keywords:** Anxiety, PTSD - Posttraumatic Stress Disorder, Depression

### 108. Synaptic Mechanisms of BNST CRF Neuron Excitability Regulating Alcohol Drinking Behavior and Anxiety

Kristen Pleit1, Jeffrey DiBerto2, Alexis Kendra2, Thomas Kash1, and Avanti Shirke2

1Weill Cornell Medicine, 2UNC Chapel Hill

**Background:** Neurons in the BNST that produce the neuropeptide corticotropin releasing factor (CRF) drive binge alcohol drinking and promote anxiety-like behavior. However, little is known about the synaptic inputs that drive BNST CRF neuron activity and the postsynaptic receptors that regulate their function, or how this critical node of circuitry is altered by chronic exposure to alcohol or stress.

**Methods:** Here, we used anterograde and retrograde neuronal tracing techniques to identify sources of direct glutamatergic synaptic input to BNST CRF neurons in mice, which included a dense projection from the paraventricular nucleus of the thalamus (PVT). We then used in vivo chemogenetic manipulations during behavioral assays to evaluate the role of PVT glutamate neurons in binge alcohol drinking and anxiety. Lastly, we evaluated the effect of repeated binge drinking on BNST CRF neurons, their PVT inputs, and postsynaptic receptors using combined ex vivo optogenetics and slice electrophysiology.

**Results:** Chemogenetic inhibition of PVT glutamate neurons blunted binge alcohol drinking but did not alter anxiety-like behavior. Repeated binge drinking increased tonic and postsynaptic neuropeptide Y 1 receptor-mediated inhibition of CRF neurons in the BNST but did not alter their excitability or PV N neuron function.

**Conclusions:** These results suggest that the PVT plays a feed-forward role in alcohol drinking, but it is not modified by chronic alcohol use. Further, they suggest that like previous results from BNST neurons in alcohol-dependent rhesus monkeys, chronic alcohol exposure increases homeostatic inhibition of BNST.
CRF neurons. Ongoing experiments are evaluating potential sex differences in the organization and function of this circuit.

Supported By: K99AA023559
Keywords: Alcohol, CRF

109. From Early Life Adversity to Adolescence Depression: White Matter Remodelling in a Translational Animal Model

Severine Farley1, Julien Grenier2, Victor Gorgievski1, Alexandre Barbe1, Wojciech Jaworski1, Ariane Bochereau1, Carlos Macedo1, Said Ghandour3, Neele Huebner4, Thomas Bienert4, Jurgen Henning4, Charbel Massaad2, Bruno Giros1, Laura Harsan5, and Eleni Tzavara1

1 Inserm, 2 University Paris Descartes, 3 Strasbourg University, 4 Uniklinik Freiburg, 5 Strasbourg University, Uniklinik Freiburg

Background: In recent years, the pathophysiology of affective disorders has increasingly been related to structural brain circuit remodelling and organizational changes, based on imaging studies in depressed adolescent patients. Myelination was proposed as one of the main mechanisms. However, no study has prospectively examined behavior, white matter imaging, and concomitant molecular changes in animal models of adolescent depression.

Methods: We established a novel mouse model of adolescent depression after early life adversity. Animals were assessed longitudinally, in a sex-dependent manner from weaning through early adulthood for several translational behavioral dimensions. The model was used to identify imaging and molecular biomarkers associated with depressive-like behavior. Myelin genes, myelin microenvironment markers and signaling pathways were investigated longitudinally, in selected regions of interest. DTI imaging was performed in adolescence, at a validated time-point of behavioral and molecular alterations.

Results: A strong phenotype of depression-like behaviors emerged in both sexes, in early adolescence. There was a clear-cut sexual dimorphism in predominant traits. DTI imaging showed widespread alterations of myelin integrity measures in limbic tracts, and in key-regions inside networks associated with negative and positive affect, cognitive control, salience, anxiety and threat. Alterations in oligodendrocyte markers and in myelin protein (MBP, PLP) expression were consistent with imaging findings. The behavioral sexual dimorphism was mirrored at the molecular/imaging level.

Conclusions: We validate a first systematic translational animal model of adolescent depression, and show functionally relevant, sex-dependent, structural connectivity changes in limbic networks.

Supported By: ERA-NET Neuron, Labex Biopsy, ANR
Keywords: Animal Model, white matter, Connectivity, Adolescent Depression, Diffusion Tensor Imaging (DTI)

110. Early Life Adversity Associates with Altered Oligodendrocyte Function and Decreased Myelination in the Anterior Cingulate Cortex of Depressed Suicides

Naguib Mechawar1, Pierre-Éric Lutz1, Arnaud Tanti1, Alicia Gasecka2, John Kim1, Marina Wakid1, Daniel Côté2, and Gustavo Turecki1

1 Douglas Institute, 2 IUSMQ

Background: Early life adversity (ELA) is a major risk factor for psychopathologies and suicide. The increasing number of neuroimaging studies reporting white matter alterations in adults having suffered from ELA suggests that child abuse can have a lasting impact on brain connectivity. However, the underlying cellular and molecular features of such white matter changes remain to be described.

Methods: To gain insight into the neurobiological impact of ELA, we performed a transcriptome-wide analysis of gene expression in samples of dorsal anterior cingulate cortex (dACC) from depressed suicides with or without a history of ELA, and psychiatrically healthy controls with no history of ELA. These well-characterized brain samples were obtained from the Douglas-Bell Canada Brain Bank. Furthermore, we used high throughput, high resolution myelin imaging by Coherent anti-Stokes Raman Scattering (CARS) to investigate myelination of individual axons within dACC white matter.

Results: Using RNA-sequencing followed by Nanostring validation, we found that a large number of genes related to myelin and oligodendrocyte function were specifically downregulated as a function of ELA. The ultrastructural analysis of white matter axons revealed that small caliber axons were less myelinated in depressed suicides with a history of ELA compared to healthy controls and to depressed suicides without ELA.

Conclusions: These results converge to highlight that ELA leads to a global and long-term impairment of oligodendrocyte function in the dACC. Considering the critical role of myelination in normal brain development, this may represent a key mechanism by which ELA may have lifelong consequences on mood and behavior.

Supported By: ERA-NET NEURON; AFSP
Keywords: child abuse, white matter, Major Depression, Suicide

111. White Matter Microstructural Variations in Adolescents with Affective Symptoms

Marie-Laure Paillere Martinot1, Helene Vulser2, Eric Artiges3, Nadege Bourvis1, Jean-Pierre Benoit1, Marie Douniol3, Richard Delorme1, David Cohen1

Supported By: ERA-NET NEURON; AFSP
Keywords: Affective Disorders, white matter,心理学

Thursday Abstracts
Ruben Miranda1, Irina Filippi1, Jean-Luc Martinot1, Herve Lemaître1, and the IMAGEN consortium4
1APHP, 2INSERM U1000, 3Erasme Hospital, Antony, France, 4www.imagen-europe.com

Background: Adolescence is a period of transition related to structural brain circuit remodelling involving myelination as one of the main mechanisms. The adolescent affective phenomenology might include major depression episodes or subthreshold pictures. It is unknown how these conditions will interplay with the trajectories of brain myelination in adolescents. We searched to identify the changes in white matter microstructure associated with affective symptoms in adolescents, and their relation to follow-up outcomes.

Methods: In a first study, the participants were extracted from the European Imagen database of community 14-year-old adolescents followed up at age 16. 96 adolescents with subthreshold depression were compared to matched controls. In a second study, 21 adolescents with a Major Depressive Episode diagnosis were compared with 22 matched controls and followed up a year later. All participants were investigated using Diffusion Tensor imaging (DTI). All had completed a diagnostic computerized interview that allows for symptom assessment. Voxel-wise comparisons were performed for DTI parameters using TBSS.

Results: In adolescents with subthreshold depression, lower global fractional anisotropy (FA) and lower regional FA in the genu of the corpus callosum (CC) and the cingulum bundles was found. In depressed adolescents, FA decreases were detected in the CC and uncinate fasciculus. Lower FA in the CC partly predicted depression outcome in adolescents with subthreshold depression.

Conclusions: Adolescents with subthreshold or full depression exhibited impaired structural connectivity that might indicate altered white matter tract maturation, and contribute to the vulnerability to affective disorders.

Supported By: ANR (French National Research Agency; grant ANR-12-SAMA-0004), Eranet–Neuron (grant AF12-NEUR0008-01 - WM2NA)

Keywords: Adolescence, Depression, Affective symptoms, Diffusion Tensor imaging (DTI), White matter microstructure

112. Pubertal Changes Affect Intrinsic Functional Brain Connectivity of mPFC and PCC Differently in Boys and Girls: A Potential Contributor to Vulnerability to Mood Disorders

Monique Ernst1, Brenda Benson1, Herve Lemaître2, Adam Gorka1, Tiffany Lago1, Eric Artiges3, Marie-Laure Paillere Martinot3, Jean-Luc Martinot2, and the IMAGEN consortium4
1NIMH/NIH, 2INSERM U1000, 3APHP, 4www.imagen-europe.com

Background: Puberty and gender critically influence brain development in adolescence. Human neuroimaging studies of puberty are difficult to conduct because of the confounding effects of age and the uneven progression of puberty. However, puberty is thought to contribute to the emergence of psychopathology, which shows unequal gender prevalence. Particularly, mood disorders show female predominance. Here, we query how puberty might influence the neural correlates of risk for mood disorders.

Methods: A community sample of 14 year-olds (n = 304, 147 males; IMAGEN-consortium) completed a resting-state fMRI study. A whole-brain corrected connectivity analysis was conducted with three seeds, mPFC, pgACC and PCC recently found associated with risk for mood problems in adolescents.

Results: Significantly different neurodevelopmental trajectories across pubertal stages emerged between boys and girls (independent of age). The mPFC showed significant puberty*sex interactions with clusters involved in cognitive control (lateral PFC), attention (inferior parietal) and social processes (inferior temporal gyrus). Connectivity strengthens in boys, but weakens in girls with pubertal progression. Similar findings emerged with the functional connectivity of the PCC, whereas the pgACC connectivity was not influenced by puberty or puberty*sex.

Conclusions: This study reveals different puberty-related maturational trajectories, in function of gender, of networks involved in vulnerability to mood disorders, as well as expression of mood symptoms. This may suggest that the mechanisms conferring vulnerability to mood problems are different in males and females, which might underlie the gender difference in prevalence rates of mood disorders. Behavioral correlations of these networks will further inform their potential role in conferring differential vulnerability to mood disorders.

Supported By: NIH, ZIAMH002798

Keywords: Resting state functional connectivity, Adolescents, risk for mood disorder, Puberty, Gender differences

SYMPOSIUM
Mismatch Negativity as a Translatable Biomarker for Schizophrenia

Thursday, May 18, 2017, 3:00PM - 5:00 PM
Aqua EF
Chair: Kiyoto Kasai
Co-Chair: Gregory Light

113. The “Other Side” of Translational Biomarker Development: Taking MMN from Academic Labs and into Real-World Settings to Predict and Monitor Response to Treatments

Gregory Light
University of California, San Diego

Background: Advances in neuroscience have transformed our understanding of impaired (and spared) brain functions in psychotic illnesses. Despite substantial progress, few if any laboratory tests have graduated to clinics to inform diagnoses, guide treatments, and monitor response. Development of more
effective treatments has been hindered by a lack of translational quantitative biomarkers that can span the brain-behavior-treatment knowledge gaps.

Methods: This presentation will show that Mismatch Negativity (MMN), an event-related potential biomarker, offers promise for improving our understanding and treatment of psychotic illnesses.

Results: Results from several proof of concept studies will be presented to show that MMN is sensitive to and/or predicts response to some pharmacologic and non-pharmacologic interventions and accounts for substantial portions of variance in clinical, cognitive, and psychosocial functioning in schizophrenia. Structural equation modeling results from N = 1415 schizophrenia patients reveal hierarchical pathways from MMN (and related measures of early auditory information processing) to cognition, symptoms, and psychosocial functioning will also be presented.

Conclusions: This collection of findings suggest that MMN can contribute to future personalized biomarker-guided treatment strategies for psychosis and support continued development of MMN for use in large-scale multi-site clinical studies of schizophrenia.

Supported By: Sidney R. Baer, Jr. Foundation, NARSAD, NIMH, VISN-22 MIRECC

Keywords: Mismatch Negativity, Biomarkers, Neurocognition, Cognitive Remediation, Cognitive Training

114. Electrophysiological, Cognitive and Clinical Profiles of At-Risk Mental State: The Longitudinal Minds in Transition (MinT) Study

Ulrich Schall1, W. Ross Fulham2, Rebekah J. Atkinson2, Patricia T. Michie2, Philip B. Ward3, Juanita Todd2, Helen Stain4, Robyn Langdon5, Renate Thienel6, Georgie Paulik6, Gavin Cooper2, and MinT (Minds in Transition) Consortium7

1University of Newcastle, School of Medicine & Population Health, 2University of Newcastle, Callaghan, Australia, 3University of New South Wales, Sydney, Australia, 4University of Durham, Durham, United Kingdom, 5Macquarie University, Sydney, Australia, 6University of Western Australia, Perth, Australia, 7University of Newcastle New, University of South Australia, Macquarie University

Background: The onset of schizophrenia is typically preceded by a prodromal period lasting several years during which sub-threshold symptoms may be identified retrospectively. Clinical interviews are currently used to identify individuals who have an ultra-high risk (UHR) of developing a psychotic illness with a view to provision of interventions that prevent, delay or reduce severity of future mental health issues. The utility of bio-markers as an adjunct in the identification of UHR individuals is not yet established. Several event-related potential measures, especially mismatch-negativity (MMN), have been identified as potential biomarkers for schizophrenia.

Methods: In this 12-month longitudinal study, demographic, clinical and neuropsychological data were acquired from 110 UHR and 65 healthy controls, of whom 87 UHR and 61 controls provided valid EEG data during passive and active auditory tasks at baseline.

Results: Despite widespread differences between UHR and controls on demographic, clinical and neuropsychological measures, ERPs did not differ between these groups. MMN amplitude was modulated by effects of cannabis, which is recognised as a risk factor for development of psychosis. Of 70 UHR at the 12-month follow-up, 7 (10%) had transitioned to a psychotic illness.

Conclusions: The statistical power to detect differences between those who did or did not transition was limited by the lower than expected transition rate. ERPs did not predict transition, with trends in the opposite direction to that predicted. In exploratory analysis, the strongest predictors of transition were measures of verbal memory and subjective emotional disturbance.

Supported By: National Health & Medical Research Council of Australia (ID: 569259)

Keywords: Schizophrenia, At-Risk Mental States, Event-related Potentials, Mismatch Negativity, Neuropsychology

115. Mismatch Negativity in Patients with Early Stages of Psychosis and in Nonhuman Primate

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Background: Mismatch negativity (MMN) is expected as a potential biomarker of schizophrenia. Previous studies reported MMN in patients with schizophrenia and MMN-like responses in animals. However, there is a gap between clinical utility of MMN in schizophrenia and neurobiology of MMN in animals. To bridge the gap, we conducted 2 studies. In study 1, we investigated association between MMN and aberrant glutamatergic neurotransmission in schizophrenia. In study 2, we investigated functional localization of MMN-like responses in nonhuman primate.

Methods: In study 1, we measured MMN and the plasma level of glutamatergic amino acids in first-episode psychosis (FEP), ultra-high risk (UHR), and healthy control (HC). In study 2, we measured electrocorticography during auditory oddball paradigms in a macaque monkey.

Results: In study 1, we found reduced MMN amplitude and increased plasma level of glutamate in FEP compared to HC. Reduced MMN amplitude was correlated with increased plasma level of glutamate in FEP. In study 2, we found MMN-like responses in the auditory cortex of the macaque monkey. The distribution of MMN-like responses was identified in each area of the auditory cortex.
**116. MMN as a Sensitive Measure of Subtle Changes in NMDAR-Mediated Glutamate Transmission in Mice**

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**Background:** Reductions in glutamate function are an important factor in schizophrenia. However, there is a paucity of animal models characterized by developmental reductions in glutamate function. Pharmacological models have been used but these typically produce only transient changes in behavior and brain function. Likewise, mice with homozygous reductions in glutamate receptor expression show stable brain and behavioral changes, but many of these phenotypes are more severe than the human disease.

**Methods:** The current study examines schizophrenia-related EEG measures in mice with a heterozygous alteration of the NMDA receptor NR1 subunit gene (NR1) that is known to result in reduced NR1 receptor expression in the homozygous mouse (NR1-/-). (NR1+/+) mice showed a 30% reduction in NR1 receptor expression and were reared after weaning in either group or isolated conditions. Outcome measures include the response to paired white noise stimuli, escalating inter-stimulus intervals (ISI) and deviance-related mismatch negativity (MMN).

**Results:** NR1+/+ mice showed no change on obligatory Event Related Potential measures including the murine P20 and N40, or measures of baseline or evoked gamma power. Alternatively, NR1+/+ mice showed a marked reduction in response during MMN task.

**Conclusions:** Data suggest that EEG response to deviant, rather than static, stimuli may be more sensitive for detecting subtle changes in glutamate function. Deficits in these heterozygous NR1 knockdown mice are consistent with data demonstrating MMN deficits among family members of schizophrenia patients and among prodromal patients. Therefore, the current study suggests that (NR1+/+) mice may be among the most sensitive models for increased vulnerability to schizophrenia.

**Supported By:** 2 R01 MH075916-05A1

**Keywords:** MMN, Mouse, NMDA

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**117. Curcumin Enhances the Extinction of a Pavlovian Fear Memory**

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**Background:** Recent evidence from our lab has indicated that a diet enriched with the naturally-occurring polyphenol compound curcumin can impair the consolidation and reconsolidation of memories associated with Pavlovian fear conditioning, a widely studied animal model of traumatic memory formation in PTSD. In the present study, we explored the effect of curcumin on the extinction of a previously established Pavlovian fear memory.

**Methods:** Sprague-Dawley rats were fear conditioned with 3 tone-shock pairings in Context A, which consisted of a chamber with grid floors, clear plastic walls, and a house light. In the first experiment, rats were fed a curcumin-enriched (1.5%) or regular chow diet for 5 days before extinction training. In the second experiment, rats received infusion of curcumin (1μg/side) or vehicle directly into the infralimbic cortex (IL) immediately following extinction training. Extinction training and testing were performed in Context B, which consisted of a dark chamber, with a black plastic floor washed with peppermint soap.

**Results:** In the diet experiment, the curcumin-fed group showed significant facilitation of fear extinction learning [F (1,28) = 18.48, p < .01] and significant enhancement of extinction retention [F (1,28) = 19.5, p < .01] compared to chow-fed controls. In the IL infusion experiment, curcumin significantly enhanced extinction retention [F (1,13) = 8.17, p = .01] relative to vehicle controls, but had no effect on extinction learning [F (1,13) = 0.093, p = .7655].

**Conclusions:** Curcumin enhances the extinction of a Pavlovian fear memory, suggesting that it may be a potential adjunct to exposure-based treatments in patients with psychiatric disorders characterized by traumatic memory formation.

**Supported By:** National Institute on Minority Health and Health Disparities of the National Institutes of Health under award number G12MD007599, Hunter RISE Minority Research Fellowship, and by an APA Dissertation Award.

**Keywords:** Fear Extinction, Curcumin, Inflammatory Signaling, Immediate Early Genes, Infralimbic Cortex

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**118. Going Beyond the Threat-detection Network in Conditioned Fear**

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Background: In an attempt to bridge the gap between fear and anxiety research, LeDoux-Pine suggested a “two systems” approach that distinguishes between two circuits involved in threat detection. One circuit mediates conscious feelings of fear and anxiety, the other responds to threat through behavioral and physiological changes. In this work, we seek to explore the conscious fear circuit and examine activations that lie in higher order cognitive areas and the cerebellum. We reanalyzed a cohort of healthy individuals, de-emphasizing the traditional fear network and highlighting the cognitive areas.

Methods: We reanalyzed data from 105 healthy subjects. Participants underwent a 2-day fear conditioning and extinction protocol in a 3T MRI scanner. We examined the BOLD response to the CS+ vs. CS- during fear conditioning, extinction, and extinction recall phases.

Results: We report brain activations that survived a whole brain FWE corrected (p ≤ 0.05) level, that are 20 voxels or more and with P-values < 0.04. During early fear conditioning, contrasts revealed significant activations within the right dorsolateral prefrontal cortex, posterior cingulate cortex, left globus pallidus, right supplementary motor area (SMA), right and left red nuclei. During late fear conditioning, significant activations were noted within the left SMA, left occipital area, right and left cerebellum.

Conclusions: Our data provide support for the involvement of higher cortical and cerebellar areas in the fear network. The extent and clinical implications of this involvement are yet to be determined. Additional analyses will be conducted to investigate the relationship between these activations, psychological, and a number of psychometric measures.

Keywords: Fear, BOLD fMRI

119. The Amygdala is Differentially Activated by Neutral Ontological Invalidity

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Background: Most fMRI studies of amygdala reactivity have focused on stimuli with arousing and/or emotional content (e.g. faces or pictures), or novel stimuli. The studies of novel stimuli have focused on stimulus novelty, i.e. events that alter the immediate stimulus surround, for example the presentation of unfamiliar face(s) contrasted with familiar ones. Few studies have examined amygdala reactivity to conceptually novel visual stimuli, i.e. images of objects that cannot exist in the real world.

Methods: 12 subjects viewed an fMRI paradigm consisting of alternating four 24 sec blocks of 12 valid (Vs) or 12 invalid (Is) pictures. Is stimuli were created in Photoshop by combing two disparate elements without any emotional content such as a toaster were utilized to create a set of Vs.

Results: Amygdala reactivity to Is (ramy: 0.39 ± 0.07; lamy: 0.24 ± 0.04) was greater than to Vs (right amy: 0.15 ± 0.06; left amy: 0.14 ± 0.04) [F(1,10) = 6.71, p = .03]. Right amygdala activation while viewing Is (0.39 ± 0.07) was greater than left amygdala activation to Is (0.24 ± 0.04), but the reaction to the Vs did not differ by side (right: 0.15 ± 0.06; left: 0.14 ± 0.04).

Conclusions: This is the first demonstration that the amygdala responds differentially to neutral ontologically invalid images, expanding our understanding of amygdala functioning.

Supported By: R01MH071467

Keywords: Amygdala, Novelty, Discrepancy

120. Patterns of Response to Fear learning: A Data-Driven Approach to a Biomarker of Generalized Anxiety Disorders

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Background: Altered fear learning processes are key mechanisms for the development of anxiety-related disorders. However, the specific patterns of the alterations are still not clear. A data-driven classification of the response may help overcome the limitations found in studies based on clinical diagnosis.

Methods: We examined anxious mood and cognitive worries associated with the skin conductance response (SCR) to a differential conditioning and extinction paradigm. Our main objective was to test whether data-driven patterns were associated with the DMS-IV classification of Generalized Anxiety Disorder (GAD). We studied 78 subjects (age 18-33, 67.9% female): 25 GAD patients and 53 healthy controls showing increased response during conditioning and decreased during extinction). GAD patients were distributed throughout clusters, increased (Cluster 2, N = 23), Decreased (Cluster 3, N = 23), and Mixed (Cluster 4, N = 11; increased response during conditioning and decreased during extinction). GAD patients were distributed throughout clusters, although Cluster 3 was significantly associated with increased cognitive worries, anxiety and depressive mood.

Conclusions: The patterns of fear learning responses were not directly associated with the clinical GAD diagnosis, but successfully differentiated cognitive and mood traits. We proposed that this data-driven approach could better inform the neurobiological basis of psychopathology.
**121. From Healthy to Pathological Anxiety: Testing the Prefronto-Subcortical Circuit in High Anxiety-Trait and Generalized Anxiety Disorder**

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**Background:** Current brain-based theoretical models of generalized anxiety disorder (GAD) suggest a dysfunction of ventromedial prefrontal cortex (vmPFC) to amygdala regulatory mechanisms. Moreover, connectivity alterations of this system are thought to be present in individuals with high anxiety-trait, as a putative expression of a neural vulnerability. However, these hypotheses have not been formally tested.

**Methods:** 29 GAD patients, 28 high- and 28 low-anxiety-trait matched individuals were scanned at rest. Between-group connectivity between the left/right basolateral amygdala and vmPFC (BLA-vmPFC) was compared in SPM. Extracted connectivity values were included in separated linear regression analyses (PCA) to analyze a BLA-vmPFCc association with clinical variables (depression, anxiety sensitivity, worry and positive/negative general affect).

**Results:** The left BLA-vmPFC showed differences across groups ($\beta = -4.18, \gamma = 11.28, \chi^2 = .03$), with patients presenting higher BLA-vmPFCc than controls and no differences between control groups. BLA-vmPFCc was negatively predicted by PANAS- in patients ($\gamma = -.38, P = .04$) and positively with anxiety sensitivity in controls ($\gamma = .40, P = .03$); high: $\gamma = .52, P = .005$).

**Conclusions:** These results support an impaired top-down emotional regulation in GAD, which might not be present in high anxiety-trait individuals. Moreover, the observed clinical associations might support hypotheses of qualitative differences in the nature of healthy vs pathological worry, with anxiety sensitivity in controls and positive affect in patients being putative risk and protective factors, respectively.

**Supported By:** Instituto Carlos III

**Keywords:** Generalized Anxiety Disorder, Anxiety, Resting state fMRI, ventromedial prefrontal cortex, Basolateral amygdala

**122. Pain-Related Negative Affect Relates to Anxious Reactivity and Anterior Insula Activity during Unpredictable Threat of Shock**

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**Background:** Negative affect is an important factor in the development and maintenance of anxiety and mood disorders. However, different components of negative affect may have distinct neural mechanisms and contribute uniquely to development of mental health symptoms.

**Methods:** Forty-three patients with depression and anxiety disorders (PT) and 40 healthy controls (HC) completed self-report measures of negative valence and underwent fMRI while exploring computer-simulated contexts with or without threat of unpredictable shock. Negative valence measures were analyzed using principal components analyses (PCA). Threat reactivity was assessed using self-reported anxiety (SA), skin conductance responses (SCR), exploratory behavior (EXP), and neural activity during the task. Voxel-wise, whole brain fMRI analyses were considered significant at p<.005, corrected for multiple comparisons.

**Results:** PCA of negative valence measures revealed two components, including general negative affect (GNA) and pain-related negative affect (PNA). The PT group evidenced greater scores on both GNA and PNA than HCs (p<.001). During threat of unpredictable shock, higher GNA related to increased posterior parietal and lateral prefrontal activity. Higher PNA related to reduced EXP, and greater SA, SCRs, and bilateral anterior insula activity. Left anterior insula activity mediated the relationship between PNA and both SCRs and anxiety ($\beta = .006, boot CI (.003, .008), and b = 3.86, boot CI (.90, 8.07), respectively$).

**Conclusions:** Distinct components may underlie negative affect, with PNA differing from GNA by contributing to anxious reactivity during anticipation of painful or threatening stimuli. The anterior insula appears to play a significant role in mediating the PNA – anxious reactivity relationship.

**Supported By:** Other

**Keywords:** Pain, Threat, Insula, Negative affect

**123. The Late Positive Potential Response to Olfactory Stimuli in Combat Veterans with Posttraumatic Stress Disorder**

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**Background:** olfaction plays a key role in emotional processing in PTSD. There is evidence that different sensory modalities (visual, auditory, tactile, olfactory) play distinct roles in emotional processing in PTSD. The current study examines pre- and post-treatment LPP (LPP) amplitude from EEG has been used to assess individual differences in emotional reactivity. There is evidence that olfaction plays a key role in emotional processing in PTSD. The late positive potential (LPP) amplitude from EEG has been used to assess individual differences in emotional reactivity. There is evidence that olfaction plays a key role in emotional processing in PTSD.

**Methods:** 28 veterans with PTSD and 28 non-veteran controls were assessed prior to a three-week exposure-based treatment. Data was available for 22 veterans following treatment. An olfactometer delivered three scents (n-butanol, rotten egg, and diesel fuel) during EEG recording.

**Supported By:** Other

**Keywords:** Generalized Anxiety Disorder, fear learning, Biomarkers, transdiagnostic traits
Results: All scents were perceived as negative in valance. The groups did not differ in LPP amplitude or behavioral ratings prior to treatment. In the veteran group, increased pre-treatment Clinician-Administered PTSD Scale (CAPS) Hyperarousal scores related to an increased early window LPP amplitude in response to the diesel fuel scent ($j = .52, p = .004$). Veterans with larger pre-treatment LPP amplitudes across scents showed larger pre- to post-treatment reduction in the CAPS Hyperarousal score, after covarying for pre-treatment CAPS Hyperarousal scores, $r(20) = -.42, p = .05$.

Conclusions: There were no group-level relationships or treatment changes with behavioral ratings or LPP amplitudes. However, a larger amplitude LPP response to negatively-valanced scents prior to treatment was related to greater improvement in hyperarousal symptoms from the exposure-based treatment. It is possible that emotional responsivity to negative odors may serve as a treatment response moderator in combat veterans with PTSD, particularly for hyperarousal symptoms.

Supported By: U.S. Army Military Operations Medical Research Program (08214003)

Keywords: PTSD - Posttraumatic Stress Disorder, olfaction, Event-related Potentials, late positive potential, Hyperarousal

124. Functional Architecture of Central Extended Amygdala Networks

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Background: The central extended amygdala (EAC)—a circuit encompassing the bed nucleus of the stria terminalis (BST) and central nucleus of the amygdala (Ce)—plays a critical role in orchestrating states of fear and anxiety and is implicated in the development and maintenance of anxiety disorders, depression, and substance abuse. Although it is widely thought that these disorders reflect the coordinated actions of large-scale neural networks, the functional architecture of the extended amygdala network remains poorly understood.

Methods: The use of higher-resolution (2-mm3; no spatial smoothing) ‘resting-state’ multiband fMRI acquired from a large sample of community-dwelling adults ($n = 185$; $n = 130$ usable; 18-40 years), cutting-edge spatial registration techniques (BBR, SyN/ANTS), and newly developed, anatomically precise seeds, allowed us to compute the intrinsic functional connectivity of the BST and Ce with an unparalleled combination of robustness and specificity.

Results: Whole-brain analyses revealed that both poles of the EACs show robust functional connectivity with one another via the sublenticular extended amygdala (‘substantia innominata’), the gray matter region encompassing the amygdalofugal pathway (all ps<.0001, Šidák corrected). Both regions also showed significant vmPFC coupling. BST showed strong connectivity with cingulate territories involved in the adaptive control of anxiety-related behavior (MCC, pgACC), while Ce showed significant coupling with neighboring amygdala nuclei, anterior hippocampus, and regions of the ventral visual processing stream involved in social processing (e.g. STS).

Conclusions: These observations provide a novel neurobiological framework for understanding a range of stress-sensitive disorders and set the stage for mechanistic work aimed at developing more effective intervention strategies.

Supported By: This was supported by the National Institutes of Health (DA040717, MH107444), University of Wisconsin, and University of Maryland

Keywords: Addiction, Amygdala, fear and anxiety, fMRI, extended amygdala (Ce/ABST)

125. Alterations in the Neurobehavioral Mechanisms of Fear Extinction and Extinction Recall in Specific Phobia

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Background: Fear extinction is the decrease in conditioned fear responses occurring with repeated presentation of a conditioned threat stimulus without reinforcement. Exposure-based treatments are thought to rely on extinction learning mechanisms. Clinical anxiety is however associated with a failure in this process, which may result in the maintenance of conditioned fear responses, and a lower response to therapy. The current study provides novel unpublished data examining whether individuals with a specific phobia (model disorder for excessive fear) show alterations in the neurobehavioral mechanisms of fear extinction and extinction recall.

Methods: Individuals aged 16-25 with a spider phobia (SP; $n = 37$) and healthy controls (HC; $n = 37$) were included. All individuals underwent a 3-day fMRI fear conditioning, extinction and extinction recall paradigm with geometrical shapes as conditioned threat (CS+) and safety (CS-) stimuli. Generalization stimuli (GS) were additionally shown during extinction recall. Fear, valence, shock expectancy and blood-oxygen-level-dependent responses were measured.

Results: Results show a trend for a smaller increase in valence for the CS+ from pre-to-post extinction in SP compared to HC ($p = .08$), suggesting impaired extinction learning in SP. Further, a smaller decrease in valence from end of extinction to recall for the CS+ was found for SP, reflecting better extinction retention ($p = .04$). At extinction recall, SP tended to reported higher shock expectancy for GS than HC ($p = .08$). Neuroimaging data show results in the fear extinction network, including the vmPFC, hippocampus, and amygdala.

Conclusions: The results point towards impaired extinction learning and reduced safety processing during extinction recall in specific phobia.

Supported By: Stichting De Weijerhorst

Keywords: Extinction Learning and Recall, Phobia, fMRI
126. Irritability and Amygdala-Ventral Prefrontal Cortex Connectivity in Children with High Functioning Autism Spectrum Disorder

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Background: Irritability is a common, highly impairing symptom among youth with high functioning autism spectrum disorder (HF-ASD) and predicts long-term adverse outcomes. Impaired processing of emotional faces, found in both autism and irritability, may lead to inappropriate social responses. Indeed, amygdala hyperactivation elicited by emotional faces has been found in autism and irritability in other diagnoses (i.e., bipolar disorder, disruptive mood dysregulation disorder). Yet, little is known about the neural correlates of irritability in HF-ASD, nor how other brain regions within amygdala networks may relate to irritability within HF-ASD. To characterize neural correlates of irritability in HF-ASD, this study investigated amygdala functional connectivity.

Methods: Children with HF-ASD (N = 33, aged 8-19 years) performed an implicit face emotion processing task during fMRI acquisition, in which participants identified the gender of faces with happy, sad, fearful, and neutral expressions. Whole-brain amygdala functional connectivity across emotions was calculated for each individual and correlated with an irritability-like measure, the Aggressive Behavior subscale of the Child Behavior Checklist (CBCL), which includes items (e.g., “temper tantrums or hot temper”) shown to comprise an irritability factor conceptualized as low threshold for anger.

Results: Whole-brain analyses revealed alterations in right amygdala to ventral prefrontal cortex functional connectivity, which correlated with the irritability-like subscale of the CBCL. Worse irritability-like symptoms related to greater amygdala-prefrontal cortex connectivity (xyz = 34,62,-2, t(31) = 3.12, p<.05, k = 80).

Conclusions: Results suggest that the neural substrates of irritability in HF-ASD include amygdala-prefrontal cortex dysfunction, providing evidence that faces may elicit emotion dysregulation in autism, which may lead to irritability.

Supported By: Autism Speaks (C.S.M) and the National Institutes of Health grants U19 HD035482 and MH066496

Keywords: High-functioning autism, Amygdala, fMRI, Functional connectivity, Irritability

127. Amygdala Response to Distress Cues and Callous-Unemotional Personality: Moderation by Trauma

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Background: Youth displaying disruptive behavior show amygdala hypo-responsiveness to fearful expressions as a function of a callous-unemotional (CU) personality (i.e., reduced guilt and empathy). This has been related to increased levels of goal-directed antisocial behavior and instrumental aggression. However, some research suggests that trauma exposure may moderate this relationship. Specifically, work has identified two groups of disruptive youth with equivalent high levels of CU-traits, but differing levels of anxiety and trauma exposure.

Methods: The objective of the first of two studies was to examine whether trauma exposure influenced the neurobiology underlying fear expression processing in 72 youth with varying levels of disruptive behavior and trauma exposure. Participants performed a gender discrimination task while viewing morphed expressions (0%, 50%, 100%, 150% fear). A linear regression analysis was performed on the BOLD data, using level of CU-traits and trauma exposure as covariates. The second study aimed at examining how the neurobiology underpinning fear expression processing predicted social behavior as a function of trauma exposure. Participants were invited back to complete a social goals task.

Results: A significant CU-traits-by-trauma exposure interaction on fear intensity processing within right amygdala was found; CU-traits were negatively associated with fear intensity modulated amygdala responses, but only in low trauma participants. Our second study suggests that stronger fear responsivity in the amygdala predicts prosocial behavior in low trauma youth, whereas stronger fear responsivity predicts non-social behavior (revenge) in high trauma youth.

Conclusions: The current data suggest that the pathophysiology associated with CU-personality may depend on trauma exposure.

Supported By: Boys Town National Research Hospital

Keywords: Disruptive Behavior Disorders, Callous-Unemotional Traits, Emotion, Fear, Trauma

128. Dysfunction in Animacy Information Processing in Adolescents with Depressive Behavior Disorders and Callous-Unemotional Traits

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Results suggest that the neural substrates of irritability in HF-ASD include amygdala-prefrontal cortex dysfunction, providing evidence that faces may elicit emotion dysregulation in autism, which may lead to irritability.
129. Addiction to Eating Was Associated with Higher Levels of BMI in Obese Patients Seeking Bariatric Surgery

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Clínica Alemana

**Background:** The concept of “food addiction” has gained interest as one of the mechanisms that may underlie the etiology of obesity. In this study we analyze the profile of obese patients looking for bariatric surgery as a treatment. The objective was to determine the relationship between eating addiction and the nutritional status (BMI) of those patients

**Methods:** 112 obese patients (61 females and 51 males) who were seeking bariatric surgery (Average BMI: 35.05) between January and March 2015 completed a structured diagnosis interview and the Yale Food Addiction Scale to measure food addiction. The questionnaire includes 25 items that evaluate eating habits

**Results:** 56 patients fulfilled addiction criteria. The non-addiction group had an average BMI of 34.2, with a significant difference with the addiction group that had an average BMI of 35.8 (p < 0.05). The analysis of variance (ANOVA) with a fixed factor of Gender (Female vs. Male) and a fixed factor Addiction (present vs. absent) revealed a significant main effect for Gender (men > women: F = 11.63; p<.001)

**Conclusions:** In an obese population candidate for bariatric surgery the presence of diagnostic criteria of addiction to food is correlated with greater BMI before the surgery. Addictive behavior tends to be more present in men than women. These observations could help to improve the description of obese patients that undergoes to surgical procedures as treatment, in the intention of finding factors, in the future, that could be related to the outcome of the surgery.

**Keywords:** Obesity, food addiction

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130. Childhood Trauma and Impulsivity in Adult Mood and Anxiety Disorders: Evidence of Behavioral Sensitization?

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**Background:** Traumatic and rewarding salient events can predispose to behavioral sensitization, a process which could underlie escalation of impulsivity and stress reactivity. In humans, this process has received limited attention. We studied associations between salient events and impulsivity, testing effect of self-reported childhood trauma and histories of suicide attempt and substance use disorder on self-reported impulsivity.

**Methods:** Participants were adults with treatment-resistant major depressive disorder (N = 140), PTSD (N = 58), anxiety disorder (N = 8), and bipolar disorder (N = 33) who completed the Inventory of Depressive Symptomatology-Self Report (IDS-SR), Childhood Trauma Questionnaire (CTQ), and Barratt Impulsiveness Scale (BIS-11). Effects were tested with general linear model (GLM) and correlation analyses.

**Results:** BIS-11 (N = 192) and CTQ (N = 186) scores were higher in our sample than normative samples of healthy volunteers (t = 5.01–38.83, p<.001, effect size d = 0.38–3.10). CTQ correlated significantly with BIS-11 (r = .17–.29); the most pronounced correlation was between BIS-11 motor impulsivity and CTQ total score (r = .31, p<.001). IDS-SR correlated with BIS-11 and CTQ. A GLM with motor impulsivity as dependent variable, and CTQ total score, IDS-SR, age, sex, history of suicide attempt, history of alcohol use disorder, and history of substance use disorder as predictor variables showed significant associations between BIS-11 and CTQ [F(7,91) = 4.51, p = .037].

**Conclusions:** Behavioral sensitization is an important process thought to underlie escalation of impulsivity and stress reactivity. We found an association between self-reported childhood trauma and trait impulsivity in a sample of psychiatric patients, consistent with trauma-induced behavioral sensitization.

**Supported By:** Johnson Family Chair for Research in Psychiatry; John S. Dunn Foundation; NIMH; facilities and resources at Michael E. DeBakey VA Medical Center.
Keywords: Affective Disorders, Anxiety Disorders, course of illness, epigenetics, Childhood Trauma

131. A New Rodent Model of Social Exclusion in Depression: Role of the Subgenual Anterior Cingulate Cortex and Anterior Insula

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Background: Major depressive disorder (MDD) is commonly associated with social impairments. Social exclusion is encoded by the subgenual anterior cingulate cortex (sgACC) and anterior insula (AI), two regions involved in MDD. We propose a model where the sgACC detects social signals and the AI regulates the information. Using a reverse translational approach, we developed a rodent version of a social exclusion task used in humans, the Cyberball, to define the role of the sgACC and AI in a lesion study.

Methods: In our task, rats interact with their peers by sending them food reward. Two groups of male Lister Hooded rats (n = 24 and n = 27) were conditioned in a custom-made apparatus composed of three operant conditioning boxes. After learning, they went through behavioral tests to investigate the impact of social inclusion and exclusion. Three lesion groups were created: sham, infralimbic (rodent equivalent of the AI) and anterior cingulate cortex (sgACC). Three lesion groups were created: sham, infralimbic (rodent equivalent of the AI) and anterior cingulate cortex (sgACC) or insular. Tests were repeated after surgery.

Results: Rats adopted a pro-social behavior by sharing food rewards, validating the social aspect of the task (n = 24, p<0.0001). Looking at the depressive-like behavior thanks to the forced swim test, there is before lesion a higher immobility time following exclusion compared to inclusion (n = 27, p<0.05).

Conclusions: Overall, these preliminary results seem to confirm the impact of social exclusion on behavior, highlighted by an increase in depressive-like behavior after social exclusion. Ongoing analyses of the data post-lesion will give us more insight on the role of the sgACC and AI and their possible interaction during exposure to social signals.

Keywords: Social Exclusion, Depression, Rodents, Insula, sgACC

132. EEG Signal after 5-Hz Transcranial Magnetic Stimulation in Patients with Comorbid Posttraumatic Stress Disorder and Major Depression

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Background: Repetitive transcranial magnetic stimulation (rTMS) delivered over left DLPFC is standard of care for pharmacoresistant major depression (MDD), and shows promise in commonly comorbid conditions, such as PTSD. Mechanisms of action of rTMS are not fully understood.

Methods: We studied potential electrophysiological signatures associated with the delivery of 5 Hz rTMS in individuals with comorbid MDD and PTSD (N = 20). We obtained the EEG recordings from 8 scalp electrodes before and after up to 40 daily rTMS sessions over left DLPFC, at 120% of resting motor threshold. We calculated EEG coherence between possible electrode pairings (8 recording sites, 28 electrode pairings). Coherence quantifies the statistical dependence of signal in two channels and can be used as a measure to estimate strength of association between the recorded sites. We used Support Vector Machine, a machine learning algorithm, to separate out pre and post rTMS EEG recordings based on the coherence.

Results: The classifier performed above chance in identifying the recording session most notably when data from Alpha, Delta and Theta bands were used (Alpha: 57.9 ± 1.6%, Delta 72.0 ± 1.5%, Theta 59.2 ± 1.7%, all significantly above chance with p<0.001). Examination of the classification algorithm revealed that rTMS reduced coherence between the L DLPFC rTMS site and sites nearby, while EEG coherence between the L DLPFC and more distant regions changed little after rTMS.

Conclusions: rTMS treatment may be associated with changes in EEG coherence closest to the stimulation site.

Keywords: EEG, PTSD depression, Coherence, Machine learning

133. Stress-Induced Decrease in Atypical Protein Kinase M Zeta (PKMz)-Mediated LTP in the Non-Human Primate (NHP) Hippocampus is Regulated by Serotonergic Signaling: A Novel Mechanism for Behavioral Correlates of Affective Disorder

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Background: Both Early-Life Stress (ELS) and chronic stress in adulthood are associated with vulnerability to mood disorder, however it’s not well understood how stressors contribute to behavioral dysregulation associated with these diseases. PKMz is critical for LTP maintenance across brain regions implicated in long-term memory, but little is known about its role in affective processing. The present study is the first characterization of PKMz expression in the NHP hippocampus. We describe behavioral correlates post-ELS, and examine effects of SERT polymorphism and SSRI- treatment to assess the role of serotonergic signaling on PKMz expression.

Methods: As infants, bonnet macaque ELS subjects (male) exposed to VFD stressor. During adulthood, female subjects
**Background:** Environmental motivational cues signal both incentive (reward/punishment) and hedonic (appetitive/aversive) accounts, with their integration often raising a conflict regarding the behavioral choice (approach/avoidance). Abnormal resolution of such goal-conflicts is evident in pathological symptoms such as diminished or excessive approach in mood disorders, or avoidance in anxiety disorders. Depicting the neural signature of motivational elements could advance domain-based brain diagnosis and treatment.

**Methods:** 46 subjects underwent fMRI while engaged in a naturalistic game-paradigm triggering motivational behavior under high- or low- goal-conflict conditions. Controlled and uncontrolled rewards and punishments allowed for further investigation of incentive and hedonic elements and regulation of behavioral choices.

**Results:** Our findings suggested a motivational regulation system involving the hippocampus and ventro-medial PFC (vmPFC), which were involved in the interactive processing of both incentive and hedonic accounts. In addition, personality profile of high reward-sensitivity and low punishment-avoidance was related to increased individual tendency to approach (vs. avoid). We further associated this reward-sensitive personality profile with the mesostriatal pathway, demonstrating greater activity in ventral tegmental area (VTA) and ventral striatum (VS) during high conflict, along with stronger hippocampus-vmPFC connectivity.

**Conclusions:** To conclude, we highlight the contribution of core regions underlying motivational processing under both reward (VTA, VS) and goal conflict (hippocampus, vmPFC) to motivational behavioral regulation and individual-differences. We further demonstrate how in their extremes, these individual-differences resemble the psychological symptomatology observed in affective disorders. Depicting the relevant circuit underlying each sub-process will eventually allow for patient- and symptom-specific treatments rather than the broad ranged pharmacological treatments offered today.

**Keywords:** Motivation, Reward, Personality, fMRI, Affective Disorders

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**135. CRP Genetic Variants and Serum Concentration in Bipolar Disorder**

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**Background:** Several recent studies have investigated the role of C-reactive protein (CRP) and other cytokines in bipolar disorder. Lesser studies have investigated the interaction of CRP genetic variants and serum CRP concentrations in bipolar disorder. In this study, we aimed to replicate altered CRP levels in different episodes of bipolar disorder and to investigate if there was an association of CRP levels with genetic variants in the CRP gene.

**Methods:** 221 bipolar patients (all episodes, 46 not medicated, 174 medicated) were genotyped by KASP assay in CRP genetic variants which have been previously shown to potentially influence peripheral CRP levels (rs1800947, rs2808630, rs1417938, rs1205). CRP levels were taken from the routine blood results. Correlations of CRP with several phenotypic and somatic variables were calculated. Differences in CRP levels between genotypes were calculated with non-parametric tests and an exploratory ANCOVA analysis. BMI did also lead to increased CRP levels but was evenly distributed throughout the genotypes.

**Results:** CC carriers of rs2808630 showed a trend towards elevated CRP levels (p = 0.051). Taken episode as covariate into account, the difference turned statistically significant (p = 0.022). There were no differences in CRP levels due to the other genotypes. But we could show significantly elevated CRP levels in manic patients compared to euthymic and depressed patients independent from genotype (p = 0.003).

**Conclusions:** Our finding of increased CRP levels in manic patients compared to depressed and euthymic patients is consistent with the results of a recent meta-analysis. There is
136. Neural Response to Implicit Emotions as Biomarkers of Clinical Response to SSRI Treatment in Depression

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Background: The search for treatment biomarkers is an important practical task, as current treatments are still ‘trial and error’, and clinical response can be assessed after weeks only. The aim of this study was to explore differential neural activation to emotional information presented below the conscious awareness level, and its prospective value in predicting response to antidepressant treatment.

Methods: Thirty two (18F:14M) patients with major depression underwent an fMRI scan before treatment with 10mg escitalopram. Clinical response was assessed after 6 weeks and defined as a 50% reduction in HAM-D. During the scan, participants performed a gender discrimination task while viewing sad and happy faces presented below the conscious awareness level and masked by a neutral face. FMRI data were analysed with FSL.

Results: After six weeks’ escitalopram treatment, 20 patients (62%) were classified as responders. Whole brain analysis revealed differences between responders and non-responders in fMRI response to sad vs happy faces across networks including thalamus, caudate, putamen, accumbens, subcallosal cortex, anterior cingulate and paracingulate, controlling for baseline depression severity. Prospective analysis by classifying one subject on the basis of response in remaining 31 volunteers, repeated separately for each of 32 subjects, allowed for correct classification in 75% cases.

Conclusions: The structures identified belong to networks involved in emotional and reward processing. Differential activation of these structures to emotional information during depression may be related to differences in treatment response. Our study supports the importance of differential activation to unconscious emotional information as a potential biomarker of treatment response.

Supported By: Medical Research Council
Keywords: Antidepressant response, Functional magnetic resonance imaging

137. Association between Habenula Dysfunction and Motivational Symptoms in Unmedicated Major Depressive Disorder

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Background: The lateral habenula plays a central role in reward and punishment processing and has been suggested to drive the cardinal symptom of anhedonia in depression. This hypothesis is largely based on observations of habenula hypermetabolism in animal models of depression, but the activity of habenula and its relationship with clinical symptoms in patients with depression remains unclear.

Methods: High-resolution functional magnetic resonance imaging (fMRI) and computational modelling were used to investigate the activity of the habenula during a probabilistic reinforcement learning task with rewarding and punishing outcomes in 21 unmedicated patients with major depression and 17 healthy participants. High-resolution anatomical scans were also acquired to assess group differences in habenula volume.

Results: Healthy individuals displayed the expected activation in the left habenula during receipt of punishment and this pattern was confirmed in the computational analysis of prediction error processing. In depressed patients, there was a trend towards attenuated left habenula activation to punishment, while greater left habenula activation was associated with more severe depressive symptoms and anhedonia. We also identified greater habenula volume in patients with depression, which was associated with anhedonic symptoms.

Conclusions: Habenula dysfunction may contribute to abnormal response to punishment in patients with depression, and symptoms such as anhedonia.

Supported By: National Natural Science Foundation of China (81501177)
Keywords: Depression, lateral habenula, Anhedonia, fMRI, punishment

138. Role of a Natural Antisense Transcript, FGF2-AS, in Affective Behavior

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Background: Anxiolytic and antidepressant effects of FGF2 are well-established, however, its angiogenic and tumorogenic potential limits its clinical use. FGF2-AS, a natural antisense RNA transcribed from the opposite strand of FGF2 regulates FGF2 expression. Therefore, FGF2-AS may also be involved in the regulation of affective behavior and potentially lack the mentioned limitations. In the present study, we investigated the effects of manipulations of FGF2-AS protein expression on depression- and anxiety-like behaviors in rats.

Methods: Male Sprague Dawley rats were used for all experiments (n = 7-14/group). FGF2-AS was overexpressed...
139. Spectral EEG Dynamics of Large-Scale Functional Network Disturbances in Depression
Alexis Whitton and Diego Pizzagalli
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**Background:** Abnormal activity in large-scale functional networks is a consistent finding in depression. In particular, functional magnetic resonance imaging (fMRI) studies have shown increased resting-state functional connectivity (rsFC) within the default mode network (DMN). However, since fMRI has limited temporal resolution, much remains unknown about how neuronal synchronization at higher frequencies contributes to these disturbances. Therefore, we capitalized on the high temporal resolution of electroencephalography (EEG) to explore the temporal dynamics of rsFC in the DMN in individuals with depression.

**Methods:** Resting-state EEG was recorded in healthy controls (n = 87), and individuals with acute (n = 63; MDD) and remitted (n = 45; rMDD) depression. rsFC within the DMN was computed in the delta, theta, alpha and beta frequencies using a measure of lagged phase synchronization. This method is thought to be accurately corrected for the effects of volume conduction as it represents the connectivity of computed intra-cortical, as opposed to scalp-based, signals after the potentially artifactual zero-lag contribution has been excluded.

**Results:** Compared to controls, those with MDD showed greater within-DMN connectivity specifically in the beta band, and this hyperconnectivity was associated with a greater severity of depressive symptoms (all ps < 0.05, FWE-corrected). No differences in DMN connectivity were observed in those with rMDD.

**Conclusions:** These findings extend our understanding of the temporal dynamics of abnormal rsFC by showing that in individuals with MDD, hyperconnectivity within this typically task-negative network, may instead be related to increases in within-network neuronal synchronization in the beta band, a frequency that is associated with active task engagement.

**Supported By:** The Scientific and Technological Research Council Of Turkey, SBAG 110S481; Loreal -UNESCO (Turkey) for women in Science Program.

**Keywords:** FGF2-AS, FGF2, antisense, depression, anxiety

140. Transcranial Direct Current Stimulation of the Default Mode Network Can Modulate Mind-Wandering Behavior after Negative Emotional Information
Tina Chou, Jill Hooley, Georgia Morgan-Fleming, and Joan Camprodon

**Background:** Mind-wandering is a cognitive process in which people spontaneously have thoughts that are unrelated to what they are currently doing. The types of spontaneous mind-wandering thoughts people have during a negative mood are similar to negative thoughts associated with depression. We investigated whether transcranial direct current stimulation (tDCS) of a default mode network brain region (associated with mind-wandering behavior) can change mind-wandering frequency and/or content after being presented with negative information.

**Methods:** Community sample participants (n = 42, data collection ongoing) were randomized to receive cathodal, anodal, or sham stimulation of the posterior inferior parietal lobule. Before and after stimulation, participants heard standardized critical comments and then completed a modified version of the go/no-go Sustained Attention to Response Task. During this task, they were randomly interrupted and asked about their thoughts. We conducted analyses to identify differences in mind-wandering frequency and content between the three stimulation groups.

**Results:** Participants who received cathodal stimulation had less of a negative mood shift after hearing criticism compared to participants who received anodal or sham stimulation. Participants who received cathodal stimulation also had more mind-wandering thoughts about the future, whereas participants who received anodal or sham stimulation had more (negative) mind-wandering thoughts about the past after hearing criticism.

**Conclusions:** tDCS of a DMN region can change the content of people’s spontaneous mind-wandering thoughts after hearing criticism. If these findings are replicated, future research can be conducted on whether cathodal tDCS of the DMN could be a treatment for depression or a preventative intervention for individuals at risk for depression.

**Supported By:** National Institutes of Health Blueprint for Neuroscience Research training grant (T90-DA022759-08) and Harvard University’s Mind Brain Behavior Graduate Student Award for interdisciplinary research.

**Keywords:** transcranial Brain Direct Current Stimulation, Mind-Wandering, Default Mode Network, Emotion Regulation
141. FOXO1, A2M and TGFβ1: Three Novel Genes Predicting Depression in Gene X Environment Interactions Are Identified Using Cross-Species and Cross-Tissues Transcriptomic and Mirmonic Analyses

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Background: Depression results from the interplay of vulnerability genes with environmental factors, a phenomenon named as ‘gene-environment (GxE) interaction’. To date, GxE interaction studies have been limited to hypothesis-based candidate genes, since genome-wide (GWAS)-based GxE interaction studies would require enormous datasets with genetics, environmental and clinical variables. We used a novel, cross-species and cross-tissues “omics” approaches to identify genes predicting depression in response to stress in GxE interactions.

Methods: We integrated the transcriptome and miRNome profiles from the hippocampus of adult rats exposed to prenatal stress (PNS) with transcriptome data obtained from blood mRNA of adult humans exposed to early life trauma, using a stringent statistical analyses pathway. Network analysis of the integrated gene lists identified the Forkhead box protein O1 (FOXO1), Alpha-2-Macroglobulin (A2M) and Transforming Growth Factor Beta 1 (TGFβ1) as candidates to be tested for GxE interactions, in two GWAS samples of adults either with a range of childhood traumatic experiences (Grady Study Project, Atlanta, USA) or with separation from parents in childhood only (Helsinki Birth Cohort Study, Finland).

Results: Six FOXO1 SNPs showed significant GxE interactions with emotional abuse in the Grady Study that survived stringent permutation analyses and were all replicated in the Helsinki study. In addition, other SNPs in all the three genes showed significant GxE interactions with emotional, physical and sexual abuse in the Grady Study.

Conclusions: We therefore provide a successful ‘hypothesis-free’ approach for the identification and prioritization of candidate genes for GxE interaction studies that can be investigated in GWAS datasets.

Keywords: Childhood Trauma, Transcriptomics, miRNAs, Animal Model, Depression

142. Levels of Immune Factors in Depression Subtypes of Treatment Resistant Depression

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Background: Previous studies indicate that immune factors regulate neuronal plasticity and stress coping and that immune dysfunction contributes to the pathogenesis of depression. The current study further explored potential links between immune factors and clinical subtypes in treatment resistant depression (TRD).

Methods: Clinical data, including, MADRS, IDS-C30, BMI, and plasma samples of 94 TRD patients were obtained from clinical trials reported previously. Melancholic and atypical depression was classified based on DSM-5 and IDS-C30 items. Patients with a MADRS Suicidal Thoughts (MADRS-ST) item score above 2 were considered to have moderate-severe suicidal ideation. Interleukin-6, interleukin-1 beta, tumor necrosis factor alpha, serum amyloid A and C-reactive protein (CRP) were measured using ELISA. Analyses were conducted using the Wilcoxon rank sum test. Networks of immune factors and clinical symptoms were also explored using pairwise Pearson or Spearman correlations.

Results: The immune factor levels were not significantly different between TRD patients with melancholic (n = 61-65), atypical (n = 10-11), and none of these two (n = 14-18) features. Patients with moderate to severe suicidal ideation had significantly lower levels of CRP (MADRS-ST>2: n = 11, 1.27±0.98; MADRS-ST≤2: n = 77, 3.42±3.80; p = 0.0453) and no significant alterations to other immune factors. There were significant correlations between BMI, CRP, IL-6, and SAA, but not between immune factors and clinical symptoms.

Conclusions: Current data suggests that, although immune dysfunction may contribute to depression pathogenesis, the immune factors studied here did not differentiate the clinical subtypes assessed in moderate to severe TRD patients. Findings on the relationship between CRP and suicidal ideation remain to be further replicated in larger cohorts.

Supported By: Janssen R & D, LLC., JNJ

Keywords: Major Depression, Treatment Resistant Depression, Cytokine, Neuroimmunology, Biomarkers

143. Cognitive Distortions Associated with Suicidal Behaviour in Bipolar Disorder I and II

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Background: Up to half of all individuals with bipolar disorder will attempt suicide and up to one in five will complete suicide.
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Thursday Abstracts

Few studies have investigated cognitive distortions in association with suicidal behaviour in bipolar patients. Aim: To examine the clinical correlates and cognitive biases associated with suicide attempts in bipolar type I and II subjects.

Methods: For this cross-sectional study, 185 participants were recruited from the Mood Disorders Program of the McGill University Health Center in Montreal, Canada. Data was gathered using structured diagnostic interviews (SCID). Ten different cognitive biases were assessed using the Cognitive Distortion Scale (CDS). Chi-square and ANOVA analyses were conducted.

Results: Both bipolar type I and II patients with a history of suicide attempts were found to have a greater number of comorbid conditions (2.50 vs. 1.04 for BPI and 3.80 vs. 2.31 for BPII), higher number of psychiatric hospitalizations (5.35 vs. 3.35 for BPI and 2.58 vs. 0.29 for BPII, p = 0.006) and a greater number of episodes (hypomanic, manic and depressed). Both bipolar type I and II patients with a history of suicide attempts had a higher overall score on the CDS (81.13 vs. 75.57 for BPI and 85.40 vs. 73.77 for BPII) as well as on each of the cognitive biases.

Conclusions: The greater number of comorbid disorders, hospitalizations and mood episodes found in bipolar disorder type II patients with suicide attempters support the notion that bipolar type II subjects suffer as much as bipolar type I. Diagnostic consideration in mood disorder populations is critical.

Keywords: Mood disorder, Suicide, cognitive distortions, Bipolar Disorder

144. Abnormal Functional Homogeneity in Late-Life Depression

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Background: Regional Homogeneity (ReHo) and Network Homogeneity (NeHo) are emerging tools in resting state MRI analyses. ReHo measures “local connectivity” as synchronization between every voxel and its 27 neighbors. NeHo measures “network connectivity” as correlation between every voxel and all other voxels within a specific specific network. Recent studies highlight default-mode (DMN) and frontoparietal network (FPN) abnormalities in late-life depression (LLD), suggesting regional dysfunction alongside wider network-level abnormalities. We hypothesized that DMN and FPN ReHo and NeHo abnormalities will distinguish depressed from healthy elders.

Methods: We examined 31 LLD patients and 43 age-matched healthy controls (M = 73.1 years, SD = 6.5). Resting state fMRI data was acquired during a 5-minute scan. We performed motion correction, regression of covariates (WM, CSF, 24 motion parameters, linear/quadratic trends), registration, smoothing (6mm), and filtering (0.01-0.1Hz). Smoothing followed ReHo calculation. NeHo was calculated as Global Brain Connectivity, restricted to DMN and FPN masks. Group differences were GRF thresholded at p = .001 voxelwise, p = .05 clusterwise.

Results: LLD patients had significantly higher ReHo in the left middle frontal gyrus, within the FPN. However, no significant results were obtained in FPN and DMN using NeHo.

Conclusions: These findings show that ReHo, but not NeHo, can distinguish LLD from healthy controls. The increased ReHo in the middle frontal gyrus confirms the key role of this area in LLD and it may be compensatory for wider network-level abnormalities, whereas the absence of NeHo effects may be a consequence of applying a-priori networks that may differ as a function of age or diagnosis.

Supported By: RO1

Keywords: Geriatric Depression, Resting state functional connectivity, Frontoparietal network, Default Mode Network

145. Neural Changes in Pain-Matrix Connectivity following Cingulotomy for Intractable Pain

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Background: Severe intractable cancer-related pain is an agonizing condition highly interfering with patients’ quality of life (QOL). Cingulotomy, a neuurosurgical ablation of the dorsal anterior cingulate cortex (dACC), had been long used to improve the condition of such patients. This procedure has been shown to provide significant pain relief with no adverse side effects. However, the impact of such lesioning on brain network organization or general cognitive functioning has not been investigated.

Methods: Eight patients with intractable cancer pain underwent bilateral cingulotomy at the Neurosurgical department, TLVMC between 11/2015 and 11/2016. Prior to and one month following the procedure, resting-state fMRI and global cognitive functioning assessment were performed. Additionally, psychological, pain and QOL questionnaires were administered. Three patients completed full pre- and post-operative assessment.

Results: Preliminary descriptive results will be presented. Immediate post-operative pain-relief was evident for all patients. Cognitive testing revealed a slight decline in attention and spatial memory. No changes were observed in executive functions, language and visuo-spatial perception. Substantial decline was evident in pain intensity and depressive symptoms, which improved QOL but not general functioning. Imaging results showed changes in functional connectivity between nodes within neural pain matrix, as well as changes in its intrinsic organization. Specifically, it seems that the thalamus had strengthened connectivity with other nodes of the network, while connectivity between the dACC and anterior insula decreased.
Conclusions: These preliminary results suggest that reduction in the affective aspect of the pain matrix may mediate pain relief reported by patients following cingulotomy.

Keywords: intractable-pain, cingulotomy, pain-matrix, dACC

146. Longitudinal Association of Pain Sensitivity and Frequency of Non-Suicidal Self-Injury in Adolescents

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Background: Nonsuicidal self-injury (NSSI) is associated with reduced pain sensitivity (PS). Existing theories posit that altered PS is a risk factor for NSSI. Cross-sectional data suggest that PS normalizes in those terminating self-injury. However, previously no study addressed the longitudinal course of PS in patients engaging in NSSI.

Methods: We addressed changes in PS and clinical symptomatology over one year comparing adolescents (12-17 years of age) with DSM-5 (section-3) diagnosis of NSSI (n = 18) to a matched controls (n = 19). NSSI and psychopathological distress were assessed using structured clinical interviews. Pain threshold, pain tolerance and pain intensity were assessed using the cold pressor task.

Results: Patients with NSSI reported a significant decrease in NSSI frequency (t(34) = 2.641, p = .012) at follow-up. Analyses revealed a significant time by group interaction on pain threshold (F(1) = 5.37, p = .021) and pain tolerance (F(1) = 4.68, p = .031), indicating decreased pain threshold and tolerance in controls compared to NSSI patients at follow-up. The relative change in NSSI frequency and pain tolerance were correlated (r (18) = -.526, p = .025), indicating that greater NSSI reduction was associated with increased pain tolerance.

Conclusions: Contrary to existing cross-sectional data, we found no evidence for a normalization of PS in adolescents reporting a reduction in NSSI frequency. The present results provide preliminary evidence for an inverse relationship between clinical improvements and changes in PS, as greater NSSI reduction was associated with increases in pain tolerance. Hypothetically, NSSI may be terminated due to a loss of effectiveness once pain tolerance is too high.

Keywords: Non-suicidal self-injury, Adolescents, pain tolerance

147. Differential Deficits in Empathy to Emotional Pain in Autism and Schizophrenia

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Background: Schizophrenia (SZ) and Autism Spectrum Disorder (ASD) are distinct disorders, but both experience social cognitive deficits, including empathy. Understanding these deficits may improve focused-interventions. We investigated several domains of social cognition in 50 Healthy Controls (HC), 49 SZ and 31 ASD.

Methods: On an empathy for emotional pain paradigm, performed as part of a social cognition battery, subjects were presented with pictures depicting individuals in either emotionally painful (e.g., funeral) or neutral (e.g., cleaning) situations during two conditions: Pain Judgment Condition (PC)- participants determined whether the individual was in emotional pain; and Gender Judgment Condition (GC). A per condition Pain Interference Index (PII) was defined as the accuracy difference between painful and neutral condition. Repeated ANOVAs were performed with Group (HC/SZ/ASD) as between-subject factor, and condition (PC/GC) as within-subject factor.

Results: PII analysis revealed a main effect of group (p = 0.01) only. Post-hoc tests revealed that ASD, but not SZ, had greater PII deficits compared to HC (p = 0.015). Analysis of social assessments demonstrated impairments in SZ on measures of emotion recognition, theory of mind and social attribution (p = 0.027 to <0.001). On an empathy questionnaire both SZ and ASD showed deficits in perspective taking and personal distress (p<0.01), but ASD only revealed deficits at empathic concern (p = 0.013) and overall empathy (p = 0.036). Correlations showed that the SZ’s higher personal distress levels correlated positively with PII in the GC (Fisher test: SZ vs. ASD; p = 0.045; SZ vs. HC; p = 0.031).

Conclusions: Results describe distinctive social cognitive deficits in SZ and ASD and provide valuable information for social skills treatments.

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Keywords: empathy, Schizophrenia, Autism Spectrum Disorder, Social Cognition, Pain perception

148. Nucleus Accumbens Functional Connectivity at Rest is Related to Alcohol Consumption in Young Adults

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Background: The nucleus accumbens (Nacc) plays an important role in the positive valuation of alcohol and the development of alcohol use disorder (AUD). We tested whether Nacc resting-state functional connectivity is associated with previous drinking behavior in young adults, and whether it predicts alcohol consumption during a one-year follow up period.
149. Curcumin Prevents Stress-Induced Increases in Innate Fear

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Background: Evidence suggests that curcumin, a compound found in the turmeric root (Curcuma longa), prevents stress-induced depressive-like behavior in rodents. However, the use of curcumin for treating anxiety has not been examined. Here we tested whether dietary curcumin blocks the effects of a social stressor on innate fear.

Methods: Adult male mice (129/EvEv) were given chow containing 1.5% curcumin or control chow for 5 days before being exposed to chronic social defeat stress or being housed in control conditions for 10 days. Social interaction was tested with an unfamiliar aggressive CD-1 mouse as the social target. One week after social defeat, innate fear in stressed (N = 10 curcumin; N = 10 control chow) and non-stressed controls (N = 10 curcumin; N = 10 control chow) was tested in the elevated plus maze (EPM) and novelty suppressed feeding (NSF) tests. Mice remained on curcumin throughout behavioral testing.

Results: Stressed mice given control chow spent less time (x = 43 seconds) interacting with the social target than all other groups (x = 143-160 seconds). In the EPM, stressed mice given control chow spent less time in the open arms (x = 26 seconds) than stressed mice given curcumin (x = 56 seconds) and non-stressed mice on control chow (x = 40 seconds). Similarly in the NSF test, stressed mice given control chow demonstrated a higher latency to feed (x = 104 seconds) than stressed mice on curcumin (x = 60 seconds).

Conclusions: Dietary curcumin blocks the effects of stress on social avoidance behavior and innate fear, suggesting that curcumin may effectively treat anxiety.

Supported By: German Research Foundation (DFG; FOR 1617)
Keywords: Alcohol, Adolescents, Nucleus accumbens, Resting state fMRI, Functional connectivity

150. Dietary Curcumin Enhances Neurogenesis-Dependent Learning

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Background: Curcumin is the active ingredient in the turmeric root and has anti-inflammatory properties and potential antidepressant effects. While curcumin may stimulate cell proliferation in the hippocampus, it is not clear if these changes in neurogenesis contribute to hippocampal-dependent learning. Based on evidence indicating that immature neurons begin modulating information processing when they are 4- to 6-weeks old, we are testing whether enhancing neurogenesis for 4 weeks with dietary curcumin promotes neurogenesis-dependent learning.

Methods: Adult male mice were given chow containing 1.5% curcumin (N = 12) or a control chow (N = 11) for 4 weeks. Mice were then tested in a contextual fear-discrimination learning task, which tests the ability to distinguish between two similar contexts. In a separate cohort of mice (N = 22), we tested whether curcumin affects the ability to distinguish between two distinct contexts. Mice remained on curcumin or control chow during behavioral testing. Cell proliferation was evaluated in all tested mice by injecting BrdU (75 mg/kg) and perfusing 2 or 24 hours later. Doublecortin-positive cells were also quantified.

Results: On the first day of testing, all mice demonstrated generalization of fear to the similar non-shock context. While curcumin-treated mice began consistently distinguishing between similar contexts on the second day of testing, this was not demonstrated by control mice until the eighth day of testing. Curcumin did not affect the ability to distinguish between two distinct contexts.

Conclusions: These results indicate that curcumin-mediated increases in adult hippocampal neurogenesis enhance contextual fear-discrimination learning, an effect that is consistent with improved pattern separation.

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Keywords: Neurogenesis, Fear conditioning, Hippocampus, Dentate Gyrus, Pattern Separation
151. Fear Extinction of Predatory Threat as an Animal Model of Posttraumatic Stress Disorder (PTSD)
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Background: Impairment of fear extinction is a characteristic of PTSD. Predator exposure in animal models mimics life threatening event experienced by these patients. Therefore, the aim of this work was to standardize an animal model of predator fear extinction.

Methods: The apparatus consisted of a home cage (25×25×25 cm) connected by a corridor (80×12.5×25 cm) to a second chamber (25×25×25 cm). First the rats were habituated to the apparatus for 10 days. Three groups were tested. Experimental (Exp; N=6): exposed to the cat (placed and contained in the second chamber) on the 11th day (10 minutes) and context re-exposed from 12th-17th (five minutes). Control 1 (CTL1; N=6): was exposed to the cat on 11th day, remained in the animal house from 12th-16th, and on 17th was re-exposed to the apparatus. Control 2 (CTL2; N=3), was not exposed to the cat and was allowed to explore the apparatus from 11th-17th (10 minutes). Time displaying risk assessment behaviors was measured.

Results: Two-way nonparametric ANOVA showed an interaction between Group and Time (F(1,8)=6.74; p<0.01). The contrast test revealed that Exp is different from CTL2 on the 12th (EXP:67.38±21.98; CTL2:1.25±2.17), 13th (EXP:46.31±31.92; CTL2:2.7±4.69), 14th (EXP:39.42±30.31; CTL2:3.6±6.23) and 15th (EXP:34.18±35.03; CTL2:4.13±7.15) days (p<0.05). Moreover, on the 17th day, the Exp (9.96±9.83) is different (p<0.05) from CTL1 (57.68±15.60).

Conclusions: The results showed that predator fear memory remains intense throughout time if the rat is not submitted to extinction. Moreover, extinction of predator fear memory takes four context exposures to occur. Future analysis of brain structures activated in these animals will bring new insights for therapeutic strategies to treat PTSD.

Supported By: FAPESP (2014/12559-5)

Keywords: PTSD - Posttraumatic Stress Disorder, Fear Extinction, Predator threat, Animal model

152. Analysis of Gene Expression in Peripheral Blood Mononuclear Cells in Naive, Depressed-Like, and Stress-Resilient Rodents Reveals Possible Peripheral Biomarkers, Correlates with Brain Function, and Possible New Drug Discovery Targets
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Janssen Research & Development, LLC

Background: Depression is an interplay between inherent genetic vulnerability and environmental insults, such as stress, as well as resiliency to such insults. Identifying peripheral biomarkers associated with depression risk or resiliency could not only help identify patients at risk to provide early treatment, but may also highlight novel molecular pathways that could lead to new preventative or maintenance medicines. We used the learned helpless model, in which rats are stress vulnerable or resilient, to explore such potential factors.

Methods: Rats were exposed to a series of inescapable shocks and then tested for helplessness, after which peripheral blood mononuclear cells (PBMC) and various brain regions were collected. Naïve controls were included. Gene expression was analyzed using the RNA-Sequencing platform.

Results: In PBMC, more changes were associated with depressed-like state, while in CNS, more changes associated with resiliency. In CNS, the amygdala had the most altered genes, a finding consistent with its function as the stress relay center. Bioinformatics revealed that genes altered in depressed-like PBMC belonged to the neuroendocrine, immune, and cellular stress pathways, with similar changes in depressed-like amygdala. Resilient amygdala genes were associated with synaptic activity, hyperactivity, and abnormal fear/stress responses. Analysis of CNS gene changes highlights several possible new drug targets for prevention or maintenance therapies to promote resilience.

Conclusions: These data suggest that stress is associated with gene expression changes in periphery indicative of cellular stress, and while stress resilient animals appear to be less impacted by such events in periphery, an active gene process in CNS is associated with resiliency.

Keywords: Depression, Learned helplessness, Resilience, Genetics, Biomarkers

153. Glutamate Homeostasis in the Adult Rat Medial Frontal Cortex is Modified by Dietary Omega-3 Fatty Acid Intake during Adolescent Development: An in vivo 1H MRS Study
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Background: Different psychiatric disorders are associated with deficits in the long-chain omega-3 fatty acid docosahexaenoic acid (DHA) and abnormalities in regional glutamate and glutamine concentrations. The present study determined the effects of dietary-induced alterations in cortical DHA accrual during adolescent development on glutamate homeostasis in the adult rat brain using 1H MRS.
Methods: From P21-P90 male rats were fed a diet with no n-3 fatty acids (Deficient, n=20), a diet fortified with preformed DHA (fish oil, FO, n=20), or a control diet (n=20). On P90 1H MRS data were acquired in the mPFC and thalamus using a 7T Bruker Biospec system.

Results: Compared with controls, PFC and RBC DHA levels were significantly lower in rats fed the n-3-free diet and significantly higher in rats fed the FO diet. In the mPFC, there was a significant main effect of diet for glutamate (p<0.006) which was significantly higher in DHA-deficient rats compared with rats fed the FO diet (+12%, p=0.003) and controls (+7%, p=0.05). There were no significant group differences for glutamine (p=0.69), and the glutamine/glutamate ratio was lower in DHA-deficient rats compared with controls (−10%, p=0.05) and rats fed the FO diet (−10%, p=0.04). In the thalamus, there were no significant group differences in glutamate (p=0.54), glutamine (p=0.78), or the glutamine/glutamate ratio (p=0.72).

Conclusions: Deficits in rat cortical DHA accrual during adolescent development recapitulates elevated glutamate concentrations frequently observed in patients with psychiatric disorders. Increasing cortical DHA accrual may represent a novel strategy to promote glutamate homeostasis.

Supported By: NIH/NIMH R01 MH107378

Keywords: Rat, Omega-3 fatty acid, Glutamate, Magnetic Resonance Imaging

154. Behavioral and Brain Network Adaptations to Chronic Stress, A Translational Study

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Background: While human magnetic resonance imaging (MRI) studies have associated depression with changes in corticolimbic circuitry morphology, function, and connectivity, preclinical studies in stress-based rodent models attribute these changes to putative molecular mechanisms.

Methods: To bridge these complementary lines of work, we used 7T structural MRI and graph theory analysis to assess regional brain volume and global structural covariance in mice exposed to unpredictable chronic mild stress (UCMS) and controls (n=12/group). We evaluated network local clustering and node degree and strength for regions showing stress-related volumetric changes. Similar analysis was performed in a human sample of Duke Neurogenetics Study participants reporting low (n=237) and high (n=299) levels of childhood trauma.

Results: UCMS mice exhibited elevated behavioral emotionality which correlated with increased amygdala and other corticolimbic region volumes. These changes were associated with increased amygdala PSD-95 (synaptic protein) density consistent with synaptic strengthening, and increased amygdala structural covariance connection number and strength, against the background of globally disrupted network clustering and modularity. A similar whole brain network alteration and amygdala-centered neural network reorganization pattern was observed in human subjects reporting high childhood trauma and increased mood symptoms.

Conclusions: The amygdalar hypertrophy and associated cellular or structural covariance changes found in rodent may indicate a greater ability of the amygdala to “drive” behavior. The cross-species convergence in structural covariance patterns suggest a conserved mechanism of stress-induced shift in priorities favoring selective strengthening of nodes involved in threat response at the expense of other behaviorally relevant functions.

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Keywords: Chronic Stress, Rodents, MRI, amygdala, structural covariance

155. Contactin-Associated Protein-Like 2 Deficiency in Juvenile Rats Recapitulates the Broad Phenotypic Spectrum in CNTNAP2-Related Disorders

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Background: CNTNAP2 mutations are associated with neurobehavioral and neuropsychiatric indications present in conditions such as ASD, IDD, ADHD, schizophrenia and bipolar disorder. Mice lacking Cntnap2 have been used to model behavioral impairments, but these findings may not fully delineate the consequences of heterozygous deficiency reported in humans. Studies of adult animals also raise the question of whether features would manifest earlier during a period that is relevant to disease onset in some CNTNAP2-related disorders.

Methods: We profiled the neurobehavioral and cellular consequences of CASPR2 heterozygous and homozygous deficiency in juvenile rats (P24 to P35 days of life) prior to the onset of behavioral seizures given that we recently reported that the consequences of ASD/IDD-related gene deficiency may differ among divergent rodent species.
Results: CNTNAP2-/- rats display altered anxiety-like behavior, impairments in select aspects of play and sensorimotor gating, repetitive behaviors and hyperactivity. Phenotypes were present almost exclusively as a function of genotype alone. CNTNAP2 +/- share a subset of these features suggesting dose-dependent penetrance. CNTNAP2 +/- and CNTNAP2-/- rats also showed decreased cortical interneuron number, with ectopic neurons present in the corpus callosum of CNTNAP2-/- rats.

Conclusions: A reduction or complete absence of CASPR2 results in strikingly different behavioral outcomes in rats compared with mice; however obsessive-compulsive-like behaviors, hyperactivity and some neuropathological alterations are shared. Taken together, these findings provide insight into the consequences of CASPR2 deficiency in a complementary rodent model, and identify the common features among CNTNAP2 genetic tools that may serve as useful outcome measures for preclinical studies.

Supported By: DP50D009134; R01HD083181; U54HD083092; Stedman West Foundation; Autism Speaks

Keywords: Rodents, ASD, Cntnap2, CDFE, Animal Behavior

156. Reduced Dysbindin Protein and Behavioral Abnormalities in Mice with a Single Point Mutation on the Schizophrenia Risk Gene DTNB1P1

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Feinstein Institute for Medical Research

Background: Dystrobrevin binding protein 1 (DTNBP1) is a schizophrenia risk gene that encodes dysbindin-1 protein, which is widely expressed synaptically in the brains of both mice and humans. Studies of post-mortem schizophrenia brains show that dysbindin protein is reduced in the prefrontal cortex and hippocampus. In this study, we examined dysbindin salt and pepper (spp) mice that have a single point mutation on the Dtnbp1 gene.

Methods: Adult (2-6 months old) male and female dysbindin spp mice were tested using multiple behavioral tests with videotracking (Noldus EthoVision XT 8.0). Western blots using SDS-PAGE were performed on homogenized brain tissue lysates. Resultado: Open field testing of locomotion and anxiety showed that spp heterozygotes and spp homozygotes did not differ from controls in their mean velocity or time spent in the center or peripheral zones. There were also no differences between genotypes for novel object recognition. In examining anxiety and depressive-like symptoms, the elevated plus maze and tail suspension tests showed no differences. In an assay of sociability, we used the chamber social interaction test and found that dysbindin spp heterozygotes (P<0.005) and homozygotes (P<0.05) spent more time than wildtype mice exploring a stranger mouse, suggesting a preference for social novelty in dysbindin spp mice. In brain tissue, we found reduced dysbindin and SNAP-25 in the frontal cortex of spp homozygotes (P<0.01), but no differences in the hippocampus.

Conclusions: Our results represent the first molecular and behavioral characterization of dysbindin spp mice, demonstrating reduced dysbindin and SNAP-25 protein in the frontal cortex of spp homozygotes.

Supported By: P50MH080173

Keywords: Dysbindin, Mouse model, SNAP-25, social interaction task, Frontal cortex

157. Novel Methods for Assessing Cell-Type Specific Differences in Human Brain

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Background: Cell-specific alterations are consistently hypothesized to contribute to mental illnesses. Many hypotheses are based on correlative data because reliable methods to assess cell-specific alterations in human brain are limited. We developed methods to be used with laser-capture microscopy to directly assess cell-specific alterations in human brain. To test their validity, we used a cohort of young and older subjects with known differences in gray matter somatostatin (SST) mRNA levels and hypothesized that SST mRNA levels in SST neurons differ between groups.

Methods: 5 young (<32 years) and 5 older (>62 years) subjects were used. Gray matter SST mRNA levels were 60% lower in the older group. Novel fluorescent in situ hybridization labeling and fluorescence detection methods were used with laser-capture microscopy to collect SST neurons from orbitofrontal cortex tissue sections, and neuronal SST mRNA levels were quantified by qPCR. Quantitative microscopy techniques were used to compare SST neuron density.

Results: SST mRNA levels in SST neurons were 26% lower (F[1,8]=4; p=0.04), and SST neuron density was 64% lower (F[1,8]=20.5; p=0.001) in older subjects. Gray matter SST mRNA levels correlated more strongly with SST neuron density (R= 0.86; p= 0.0003) than neuronal SST mRNA levels (R= 0.55; p= 0.045).

Conclusions: These novel methods provide a reliable way of directly testing cell-specific hypotheses in brain samples between human subject groups. In addition to aging, lower gray matter SST mRNA levels are reported across mental illnesses. Future studies will inform on whether lower SST mRNA levels between brain conditions occur by common mechanisms.

Supported By: NIH RO1 MH093723-05

Keywords: Brain Aging, Somatostatin Neuron, Laser Capture Microdissection

158. Decoding Brain Epigenome Maps with Broad Histone H3K4me3 Domains: Discovering Functional Epigenetic Patterns and Their Dynamics in Gene Regulatory Networks

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**Background:** Only few histone modifications have been mapped in human brain. Trimethylation of histone H3 at lysine 4 (H3K4me3), an extensively-studied histone modification, is known to mark the transcription start sites (TSS) of active gene promoters. Typical H3K4me3 mark is usually confined to a punctate interval of 1-2 kb pairs with high signal density around the TSS. Regulators of H3K4me3 mark are significantly associated with the genetic risk architecture of common neurodevelopmental disease, including schizophrenia and autism. However, there is very little information on the importance of the breadth of an H3K4me3 enrichment locus in normal and diseased human brain.

**Methods:** Here, through integrative computational analysis of epigenomic and transcriptomic data based on next generation sequencing, we investigated, at base pair resolution on a genome-wide scale, H3K4me3 landscapes of FACS sorted neuronal NeuN+ and non-neuronal nuclei NeuN- in human postmortem, non-human primates (chimpanzee and macaque) and mouse prefrontal cortex (PFC), and nucleated blood cells.

**Results:** The neuronal broad histone H3K4me3 peaks in the present study were enriched for genes regulating neuronal connectivity and signaling, including many ion channels, and synaptic plasticity and learning and memory. Interestingly, cross-species comparison of broadest H3K4me3 peaks in NeuN+ neurons of the adult cortex identified many genes regulating excitatory glutamatergic neurotransmission and dopaminergic pathways with a conserved broadest peak profile in human, non-human primates and mouse.

**Conclusions:** Exploration of spread and breadth of lysine methylation markings in specific cell types could provide novel insights into epigenetic mechanisms of normal and diseased brain development, aging and evolution of neuronal genomes.

**Supported By:** National Institutes of Health

**Keywords:** Epigenome, Human Postmortem Brain, gene networks, chromatin

159. The Largest Number of Cocaine-Induced Changes in Chromatin Modifications Are Associated with Increased Expression and 3D Looping of Auts2

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**Background:** Exposure to drugs of abuse alters the epigenetic landscape of the brain’s reward regions such as the nucleus accumbens (NAC). We investigated how a combination of chromatin modifications affects genes that regulate responses to the psychostimulant drug of abuse, cocaine. A subset of loci showed strong clustering of cocaine-induced chromatin modifications, including Autism-candidate 2 (Auts2), a gene strongly linked to cognitive disease and human evolution.

**Methods:** We combined chromosome conformation capture approaches (4C and 3C) with behavioral paradigms relevant to cocaine phenotypes. Cell type specific functions were assessed by FACS-sorting viral-mediated overexpression into Cre-dependent mouse lines.

**Results:** We observed that Auts2 gene expression is increased repeated cocaine administration, specifically in D2-type medium spiny neurons (MSNs) of the NAC, an effect seen in male but not female mice. Auts2 mRNA expression was upregulated postmortem in NAC of male human cocaine addicts. We obtained evidence that chromosomal loopings, bypassing 1,524 kb of linear genome, connect Auts2 to the Calneuron 1 (Caln1) gene locus under baseline conditions. These loopings were severely disrupted after chronic cocaine exposure, resulting in increased expression of both genes in D2 MSNs. We show that uniform expression induces reduced binding of CTCF chromosomal scaffolding protein at the Auts-Caln1 loop base, together with up-regulated expression and open chromatin-associated histone methylation. Cell type-specific overexpression of Auts2 or Caln1 in D2 MSNs confirmed that both genes play a role in cocaine reward.

**Conclusions:** Drug-induced alterations of neuronal (3D) genome organization could destabilize higher order chromatin involved in synergistic regulation of reward-regulating genes.

**Supported By:** P01 DA008227 (EJN); K99DA042111 and a NARSAD Young Investigator Award (ESC)

**Keywords:** Epigenetics, cocaine, Nucleus Accumbens, chromosomal conformation

160. NACR Mediates Nicotinic Acetylcholine Receptor Expression and Function in the Brain

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Janssens

**Background:** Neuronal nicotinic acetylcholine receptors (nAChRs) participate in diverse aspects of brain function and mediate behavioral and addictive properties of nicotine. Neuronal nAChRs assembly is tightly regulated and their recombination expression in other cell types is minimal due to the lack of unknown neuronal factors required for nAChR biogenesis. In the present study we screened a genomic library to identify neuronal factors required for nAChR biogenesis.

**Methods:** Plasmids representing all human transmembrane proteins were individually co-transfected in 384 plates with cDNAs encoding α7 nAChR. For screening, channel activity was assessed by acetylcholine-evoked calcium influx and further analysis used whole-cell patch clamp. Autoradiography with specific nAChR ligands was used to detect expression of specific nAChR subtypes in brain slices from mice. Behavioral
testing for cognitive function and reward-related behavior of WT and NACHO knock out mice was done at a CRO, Psychogenics.

Results: From our genomic screen, we identified NACHO as an essential chaperone for the functional expression \( \alpha 7 \) nAChR in both recombinant systems and native brain tissue. NACHO also increased expression of \( \alpha 4 \beta 2 , \alpha 3 \beta 2 , \alpha 3 \beta 4 , \) and \( \alpha 6 \beta 2 \) containing nAChRs in both recombinant and native tissue. NACHO knock out mice showed deficits in Y-maze alternations, the Morris Water Maze, and nicotine conditioned place preference.

Conclusions: NACHO mediates the assembly of a diverse class of nAChR family in the brain. NACHO knockout mice show profound deficits in the expression of the major nAChRs in the brain and also show deficits in cognitive function and reward-related behavior, compatible with the loss of nAChR expression.

Keywords: nicotinic receptor, NACHO, TMEM35, Nicotine Dependence, Cognitive Neuroscience

161. A Pilot Screen for Neurite Growth-Promoting Compounds: A Comparison between Human iPS and Primary Rodent Neurons

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Background: Human induced pluripotent stem (iPS) cells are reprogrammed adult human cells that have stem cell-like capacity. The ability to differentiate these cells into neurons of various types and grow them in culture may allow us to better understand psychiatric disease processes. Neurite outgrowth is a well-studied biologic capacity. The ability to determine cell-type specific molecular dysfunctions. Reduced representitive bisulfite sequencing (RRBS) is a widely used technique for the analysis of genome-wide methylation patterns, in regions of high CpG content, at the level of a single nucleotide. There are, however, many disadvantages associated with traditional RRBS, including its reliance on costly methylated adaptors, fragmentation of libraries during bisulfite conversion, high gDNA input requirements, as well as duplicated reads.

Methods: Here we describe a simple, PCR-amplification directed RRBS pipeline that ameliorates the need for adaptor based library construction. Briefly, our PCR-amplon RRBS protocol involves three steps, MspI digestion, bisulfite conversion and PCR amplification with uniquely designed primers integrating locked nucleic acid technology.

Results: Preliminary sequencing data is of comparable quality as RRBS employing traditional library construction. In extension to this, our pipeline is capable of amplifying bisulfite converted gDNA from \( \sim 350 \) pyramidal cells captured from post-mortem samples using Laser Capture Microdissection.

Conclusions: The utility of this protocol is its compatibility with microdissected post-mortem samples, thereby allowing for the investigation of cell-type specific alterations in DNA methylation underlying various illnesses.

Supported By: FRQS; CIHR

Keywords: Human Postmortem Brain, Epigenetics, Single Cell Type Sequencing, Laser Capture Microdissection

162. LCM-RRBS: A Novel PCR-Amplicon Based Method Compatible with Post-Mortem Samples

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Background: Throughout neurodevelopment, spatiotemporal control over gene expression by epigenetic regulation of promoters and enhancers results in a multifaceted complexity and heterogeneity of cell types within the mammalian brain. Each discrete cellular population is differentially influenced by extrinsic signals from their local environments and neighbouring cells. Thus, while a wealth of studies have investigated transcriptomic and epigenomic alterations underlying the neurobiology of psychiatric illnesses, the use of bulk-tissue homogenates have masked their ability to determine cell-type specific molecular dysfunctions. Reduced representitive bisulfite sequencing (RRBS) is a widely used technique for the analysis of genome-wide methylation patterns, in regions of high CpG content, at the level of a single nucleotide. There are, however, many disadvantages associated with traditional RRBS, including its reliance on costly methylated adaptors, fragmentation of libraries during bisulfite conversion, high gDNA input requirements, as well as duplicated reads.

Methods: Here we describe a simple, PCR-amplification directed RRBS pipeline that ameliorates the need for adaptor based library construction. Briefly, our PCR-amplon RRBS protocol involves three steps, MspI digestion, bisulfite conversion and PCR amplification with uniquely designed primers integrating locked nucleic acid technology.

Results: Preliminary sequencing data is of comparable quality as RRBS employing traditional library construction. In extension to this, our pipeline is capable of amplifying bisulfite converted gDNA from \( \sim 350 \) pyramidal cells captured from post-mortem samples using Laser Capture Microdissection.

Conclusions: The utility of this protocol is its compatibility with microdissected post-mortem samples, thereby allowing for the investigation of cell-type specific alterations in DNA methylation underlying various illnesses.

Supported By: FRQS; CIHR

Keywords: Human Postmortem Brain, Epigenetics, Single Cell Type Sequencing, Laser Capture Microdissection

163. Mood-Associated Gsk3β/Fxr1P Pathway Regulates Homeostatic Plasticity

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Keywords: neurite outgrowth, hiPSC, high-throughput drug screening, neural phenotypes, disease modeling
Background: Fragile X mental retardation syndrome-related protein 1 (Fxr1P) is a RNA binding protein identified as a potential risk factor for several mental illnesses. Recently we demonstrated that Fxr1P can be directly phosphorylated by Gsk3β and regulated in response to treatment with mood stabilizer drugs. Furthermore, interaction between human functional polymorphisms in the GSK3B and FXR1 genes contributes to mood regulation. However, the mechanism behind mood regulation by Gsk3/Fxr1P pathway remains unclear.

Methods: We used a combination of CRISPR/Cas9 mediated knockout and viral mediated overexpression to modulate the expression of Fxr1P and Gsk3β directly in the prefrontal cortex of adult animals. KORD-mediated chemogenetic was used to interrogate the contribution of neuronal activity to behavioral phenotypes. Further characterization of underlying cellular mechanisms was conducted using acute live brain slices and primary cortical neuron cultures.

Results: Inactivation of Gsk3β or overexpression of Fxr1P resulted in reduced neuronal activity accompanied by decreased “anxiety-like” behavioral phenotypes. Reduction of neuronal activity using Gi-KORD led to similar behavioral outcomes. Further in vitro and in vivo characterization revealed the engagement of the Gsk3β/Fxr1P pathway in regulation of homeostatic synaptic plasticity.

Conclusions: These observations suggest that drugs acting on the Gsk3β/Fxr1P pathway could regulate homeostatic plasticity. Targeting this pathway in different neuronal networks, using genome editing or pharmacological agents, may prove useful not only for mood disorders and schizophrenia but also autism, epilepsy and chronic pain, in which abnormal homeostatic plasticity may be implicated.

Keywords: Gsk3, Fxr1P, homeostatic plasticity, anxiety, bipolar disorder

164. Brain-Derived Neurotrophic Factor Splice Variants Differentially Impact CA1 and CA3 Dendrite Complexity and Spine Morphology in the Hippocampus

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Background: Brain-derived neurotrophic factor (BDNF) is an activity-dependent neurotrophin critical for hippocampal plasticity. BDNF encodes multiple transcripts with alternative 5' untranslated regions (5'UTRS) that display activity-induced targeting to distinct subcellular compartments. While individual Bdnf 5'UTR transcripts influence dendrite morphology in cultured hippocampal neurons, it is unknown whether Bdnf splice variants impact dendrite arborization in functional classes of neurons in the intact hippocampus. Moreover, the contribution of Bdnf 5'UTR splice variants to dendritic spine density and shape has not been explored.

Methods: We analyzed the structure of CA1 and CA3 dendrites, as well as CA1 apical spines, were imaged using confocal microscopy and reconstructed using Neurolucida. We analyzed changes in dendrite length and branching as well as changes in spine density and morphology.

Results: Bdnf Ex2 and Ex6 transcripts significantly contributed to dendrite morphology in CA1 and CA3 neurons. While Bdnf-e2 mice showed increased branching proximal to the soma in CA1 and CA3 apical arbors, Bdnf-e6 mice showed decreased apical and basal dendrite complexity in both neuron populations. Analysis of spine morphology on Bdnf-e6 CA1 dendrites revealed changes in the percentage of differently sized spines on apical, but not basal, branches.

Conclusions: Disruption of BDNF from individual promoters differentially impacts hippocampal dendrite morphology. These results provide further evidence that Bdnf splice variants generate a spatial code that mediates the local actions of BDNF in distinct dendritic compartments.

Supported By: T32MH01533037; RO1MH105592; Lieber Institute

Keywords: BDNF, morphology, dendrite branching, Hippocampus, splice variants

165. Differing Expression Pattern of Epidermal Growth Factor (EGF) and Immune System Markers between Schizophrenia and Mood Disorder in the Dorsolateral Prefrontal Cortex

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Background: Immune activation at maternal, foetal and postnatal levels operates as a known risk factor for psychosis. How this is transduced is unknown but one plausible disease mechanism may be through immune activation perturbing central nervous system growth factor systems, such as the epidermal growth factor (EGF) system critical to neuronal proliferation, differentiation, maturation and plasticity, altering neurodevelopment and synaptic function.

Methods: The expression of 114 candidate genes from EGF and immune system markers between schizophrenia and mood disorder patients and healthy controls (n=68), using the Fluidigm Biomark qRT-PCR platform.

Results: Seventy genes were significantly differently expressed between diagnostic groups. In comparison to healthy controls 60 genes were differentially expressed in schizophrenia and 14 in the mood disorder group. The genes included EGF system components – BTH, HBGF, NRG and ERBB4; complement – C1QB, C1QC, C3 and C4A; cytokines and receptors – IFNA1, IFNAR1, IFNGR2, IL8, IL12A and TNFRSF1A; and downstream signalling molecules – CHUK, IKBKAP, NFKB1, JAK1, STAT1, GRB2 and GSK3B. Collectively these differentially expressed genes predominately belong to ERBB signalling and associated MAPK, PI3K and MTOR...
pathways along with immune pathways involving TLR, TNF, NFkB and JAK-STAT signalling. The expression of most of the genes was decreased in the patient groups compared to control subjects.

**Conclusions:** The different pathway gene expression changes between schizophrenia and mood disorders may reflect variant pathological processes involving immune and EGF system signalling between these sets of disorders.

**Supported By:** NWMH seed grant

**Keywords:** Schizophrenia, Epidermal Growth Factor System, Immune system, Human Postmortem Brain, Mood disorders

166. Expression of GABA Neuron Markers across the Cortical Visuospatial Working Memory Network in Schizophrenia

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**Background:** In the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia, alterations in GABA neurons appear to be selective for the separate subsets that express parvalbumin (PV) or somatostatin (SST), whereas calretinin (CR)-containing neurons appear to be unaffected. For example, mRNA levels of PV, SST, two gene products [μ-opioid receptor (MOR) and LHX6 transcription factor] expressed by both PV and SST neurons, and KCNS3, a PV neuron-selective potassium channel subunit, are all lower in the DLPFC of schizophrenia subjects. In addition, GAD67 expression is lower in PV neurons. We tested whether this subset-selective pattern of GABA neuron alterations is conserved across cortical areas in the visuospatial working memory network, possibly contributing to working memory impairments in schizophrenia.

**Methods:** Levels of eight transcripts that reflect the subset-selective alterations in GABA neurons were quantified in the DLPFC, posterior parietal cortex, and primary and secondary visual cortices from 20 matched pairs of schizophrenia and unaffected comparison subjects using qPCR. Effects of diagnosis, cortical area and diagnosis × area interaction were tested using two-way analysis of variance models and Bonferroni correction for multiple comparisons.

**Results:** Diagnosis effect was significant for GAD67, PV, SST, KCNS3 and MOR mRNAs without a significant effect of diagnosis × area interaction. Diagnosis did not have a significant effect on transcript levels of LHX6, CR or vasoactive intestinal polypeptide, which is expressed by CR neurons.

**Conclusions:** These findings indicate that the subset-selective pattern of alterations in PV and SST GABA neurons in schizophrenia is conserved across cortical areas within the visuospatial working memory network.

**Supported By:** NIMH: P50 MH103204; JSPS: 15H01280, 16H05372

**Keywords:** Postmortem human brain, Frontoparietal network, Early visual cortices, Parvalbumin neuron, Somatostatin neuron

167. A Neurobiological Basis for Behavioral Therapy Using Drosophila

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**Background:** Novel and effective pharmacotherapeutic treatments for psychiatric disease have proven elusive, but many advances have been made in treating mental illness with behavioral approaches. A molecular basis for how behavioral therapies work could open new avenues for intervention. Using sleep as a tool to study behavioral modification, we have developed an innovative Drosophila model to yield previously unattainable insights into how a behavioral therapy works with cellular and molecular resolution.

**Methods:** Light and temperature changes were used to control sleep timing in short-sleeping mutants or aged flies. A molecular/circuit basis of behavioral sleep modification was studied with multiple genetic approaches. Sleep in flies was measured with the Drosophila Activity Monitoring system.

**Results:** Behavioral manipulations alone improve sleep in Drosophila genetic sleep mutants, and enhance sleep drive sufficient to overcome direct activation of wake promoting brain regions. Using tools in the fly allowing precise control over neuronal subpopulations, we are mapping the circuits involved in mediating behavioral sleep modification. This model is also being exploited to redefine interventional targets for restoring sleep and memory loss with aging. Drosophila exhibit increased sleep fragmentation with aging, which is reversible with behavioral intervention alone.

**Conclusions:** Strides have been made in treating psychiatric disease through behavioral approaches but little is known regarding the neurobiological basis of behavioral therapies. We have developed a model to probe mechanisms of a behavioral therapy in a genetically tractable system. Our results suggest behavioral manipulations can be leveraged as a novel approach to study sleep biology and identify new treatment targets.

**Supported By:** NINDS K08 NS090461; Burroughs Wellcome Career Award for Medical Scientists; Alfred P Sloan Fellowship in Neuroscience

**Keywords:** Sleep, Drosophila, Insomnia, cognitive behavioral therapy, Aging

168. Transcranial Direct Current Stimulation (tDCS) Combined with Computerized Cognitive Training to Enhance Memory in People with Amnestic Mild Cognitive Impairment (aMCI): Preliminary Results from a Pilot Randomized Controlled Trial

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**Background:** Many advances have been made in treating mental illness with behavioral approaches. A molecular basis for how behavioral therapies work could open new avenues for intervention. Using sleep as a tool to study behavioral modification, we have developed an innovative Drosophila model to yield previously unattainable insights into how a behavioral therapy works with cellular and molecular resolution.
Background: Currently, there is no effective intervention available for people at increased risk for dementia, i.e., with aMCI. While recent reviews have highlighted promising results for cognitive training (CT), RCTs have shown modest efficacy. Transcranial direct current stimulation (tDCS) is a safe, non-invasive technique which can enhance cognitive functioning. This study examined whether tDCS + CT is more effective than CT alone for improving memory.

Methods: A double-blind, sham-controlled, parallel group RCT. Participants received either Active tDCS + CT or Sham tDCS + CT during computerized CT over 15 sessions over 5 weeks. The primary outcome measure was the California Verbal Learning Test 2nd Edition (CVLT-II). Outcomes were administered at baseline, end treatment and 3 month follow-up.

Results: Preliminary data from 39 participants will be presented. For the primary outcome, repeated measures analysis of variance showed a significant main effect of Time [F(2,74) = 36.1, p < .001], though non-significant Time by Condition interaction effect [F(2,74) = 1.83, p = .168]. Over the entire sample, there was a large sized memory improvement from baseline (mean T Score = 45.5 (SD = 8.95) to 3 month follow-up (mean T Score = 58.2 (SD = 10.6). There was a statistical trend for greater memory improvement with Active tDCS + CT compared to Sham tDCS + CT [t (1,37) = 1.97, p = .057].

Conclusions: Preliminary results indicated large sized memory improvement at 3 month follow-up with active or sham tDCS combined with CT. These results support the utility of computerized CT for improving memory in aMCI.

Supported By: Center for Healthy Brain and Ageing, Alzheimer's Australia

Keywords: memory, amnestic mild cognitive impairment, transcranial direct current stimulation, cognitive training, clinical trial

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169. Modulation of Anxiety-Relevant Neural Circuits in Generalized Anxiety Disorder: A Novel Cholinergic System Pharmacotherapy Approach

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Background: There is robust evidence for pharmacological serotonergic and GABAergic normalisation of key amygdala-centred network reactions to threat stimuli; however, these anxiolytic medications can have problematic side effects. There has been little investigation into cholinergic systems as alternate modifiers of anxiety-related amygdala networks.

Methods: The current study administered a novel α7 nicotinic acetylcholine negative allosteric modulator, BNC210, to individuals with Generalized Anxiety Disorder (GAD) prior to engagement in a series of threat-related tasks. 24 Participants completed an emotional faces task and a human translation of a rodent defence task (the Joystick Operated Runway Task, JORT) whilst in an fMRI scanner, in this four-way crossover, double-blind randomised controlled Phase 2a trial.

Results: Results demonstrated that BNC210 reduced amygdala reactivity to fearful faces relative to placebo. In addition, BNC210 reduced the intensity of avoidance behaviour, relative to placebo, in the JORT task.

Conclusions: These results suggest that the function of anxiety-related neural circuits and anxiety-related behaviours can be altered through modulation of cholinergic neurotransmission, highlighting the potential of this system as a novel anxiolytic pharmacological approach for GAD.

Supported By: Bionomics

Keywords: Generalized Anxiety Disorder, Neuroimaging, Translational research, Clinical-Trial, Amygdala

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170. 5 Hz Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder Comorbid with Major Depressive Disorder

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Background: Standard clinical repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) uses 10Hz stimulation to the left dorsolateral prefrontal cortex, yet little is known about the benefits of rTMS for diagnostically complex patients. Posttraumatic stress disorder (PTSD) is commonly comorbid with MDD, and while rTMS has been shown to alleviate PTSD symptoms, ideal parameters remain unclear. We conducted an unblinded study of 5Hz rTMS for comorbid PTSD+MDD and hypothesized stimulation would reduce symptoms of both disorders.
Methods: Participants (N=40) were outpatients with comorbid PTSD + MDD, with at least moderate symptoms despite ≥6 weeks of stable treatment. 5Hz rTMS included 40 daily sessions followed by a 5-session taper. PTSD and MDD symptoms were measured using the PTSD Checklist (PCL-5) and Inventory of Depressive Symptomatology, Self-Report (IDS-SR), respectively. Baseline-to-endpoint changes were characterized using paired-sample t-tests, with Pearson correlations evaluating the relationship between PTSD and MDD changes.

Results: The intention-to-treat population (i.e., consented and completed ≥1 session) included 35 participants. Stimulation significantly reduced PTSD symptoms from baseline (52.2±13.1) to endpoint (34.0±21.6; p<.001). Twenty-three (65.7%) achieved meaningful clinical response, and 17 (48.6%) dropped below threshold criteria. MDD symptoms also decreased from baseline (47.8±11.9) to endpoint (30.9±18.9; p<.001). Fifteen (42.9%) demonstrated clinical response and 12 (34.3%) remitted. Changes in PTSD and MDD were highly correlated (r=.9, p<.001).

Conclusions: Significant and clinically meaningful reductions in both MDD and PTSD symptoms were observed following stimulation. The efficacy of 5Hz rTMS for both symptom domains indicates a need for future controlled studies in this comorbid population.

Supported By: US Dept of Veterans Affairs IK2 CX000724; Investigator-initiated grant from Neuronetics, Inc.

Keywords: Repetitive Transcranial Magnetic Stimulation, PTSD - Posttraumatic Stress Disorder, Major Depressive Disorder (MDD)

171. A Randomized Controlled Dose-Ranging Study of Intranasal Administration of Neuropeptide Y in Patients with Posttraumatic Stress Disorder

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Background: Anxiety and trauma-related disorders are among the most prevalent and disabling medical conditions in the U.S. We examined the tolerability and anxiolytic efficacy of neuropeptide Y (NPY) administered via an intranasal route in patients with posttraumatic stress disorder (PTSD).

Methods: This randomized, cross-over, dose-ranging study enrolled 24 individuals with PTSD according to an escalation algorithm into one of five dose cohorts as follows: 1.4 mg (n=3), 2.8 mg (n=6), 4.6 mg (n=5), 6.8 mg (n=6), and 9.6 mg (n=6). Each individual was dosed with NPY/placebo on separate treatment days one week apart in random order under double-blind conditions; Procedures included baseline anxiety/PTSD symptom ratings, nasal administration of NPY/placebo, and trauma script symptom provocation followed by multiple symptom ratings over the next two hours and 1, 2 and 7 days later. Occurrence of adverse events represented the primary tolerability outcome. The difference between treatment conditions on anxiety as measured by the Beck Anxiety Inventory (BAI) and the State-Trait Anxiety Inventory (STAI) immediately following the trauma script represented the principal efficacy outcomes.

Results: NPY was well tolerated up to and including the highest dose. There was a significant interaction between treatment and dose; higher doses of NPY were associated with a greater treatment effect, favoring NPY over placebo on BAI score [F(1,20)=4.95, p=0.038].

Conclusions: These data suggest that intranasal NPY is well tolerated up to 9.6 mg and may be associated with anxiolytic effects. Additional studies exploring the safety and efficacy of NPY are warranted.

Supported By: The current project was supported by the Icahn School of Medicine at Mount Sinai and by the National Center for PTSD.

Keywords: Neuropeptide Y, PTSD - Posttraumatic Stress Disorder, Resilience, Anxiety, Novel treatments

172. Controlled Clinical Trial of Magnetic Seizure Therapy (MST) and ECT: A Medication-Free Study

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Background: The aims were: 1) Evaluate the feasibility and safety of magnetic seizure therapy (MST) in treating major depressive disorder (MDD) in the Egyptian population. 2) Compare the efficacy of MST in MDD to that of ECT without the confounding effect of medications; 3) Compare the cognitive adverse effects of MST to that of ECT.

Methods: After IRB approval and informed consent, adult patients who were not on antidepressant treatment for 6 weeks and matched for demographic characteristics were assigned to be treated with either Unilateral or bilateral ECT with Thymatron IV (Somatics, Venice, FL, USA) and pulse width of 0.5msec, or HD-MST with Magstim Theta device (Wales, UK). The MST stimulation was at 100% of device output, frequency 100Hz, and train duration of 10 seconds at vertex placement. Efficacy was primarily assessed by Hamilton Depression Scale-21 and cognitive side effects were assessed by Time to Reorientation (TRO) and a neuropsychological battery (pre-post course).

Results: Sixty depressed patients with MDD (DSM-IV) were enrolled. There was no difference in depression improvement between MST and ECT group. In addition, MST had significantly less cognitive adverse effects and much faster TRO of 1.8min (SD=0.36) compared to both unilateral and bilateral ECT. Limitations: include that the study were matched for demographics but randomization or blinded.
Conclusions: MST was feasible and safe in this population. MST was also efficacious in treating MDD with less cognitive adverse effects than ECT. Larger studies are needed to replicate these findings before adoption in clinical care.

Supported By: Psychiatry, Neurology and Neurosurgery Center, Tanta University, Egypt

Keywords: Magnetic Seizure Therapy, Treatment Resistant Depression, Affective Disorders, Electroconvulsive therapy, Depression

173. The Incremental Predictive Validity of Rostral Anterior Cingulate Cortex Activity in Relation to Treatment Response in Depression: Evidence from the EMBARC Study

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Background: Theta activity localized to the rostral anterior cingulate cortex (rACC) has previously been shown to predict treatment response across different interventions. However, prior studies have not evaluated whether this prognostic predictor has incremental predictive validity above and beyond other much more inexpensive and easily administered measures (e.g., clinical and demographic) previously shown to predict treatment response.

Methods: We examined whether rACC theta activity (4.5-8Hz) - assessed via Low Resolution Electromagnetic Tomography – predicted depressive symptom improvement (Hamilton Rating Scale for Depression) within the EMBARC study, a multi-site randomized clinical trial of sertraline vs. placebo for major depressive disorder (n = 274). rACC theta activity was assessed at two time-points (baseline and 1 week later).

Results: Hierarchical linear modeling indicated that higher theta rACC activity at both baseline (t=-3.05; p=.003) and week 1 (t=-2.14; p=.03) predicted greater depressive symptom improvement at end point, even when controlling for relevant clinical (depression severity and chronicity, anxiety symptoms) and demographic (age, race, gender, marital and employment status) variables previously linked to treatment response. There were no significant differences between treatment conditions in rACC-outcome associations.

Baseline and week 1 theta rACC activity were significantly correlated in both the sertraline (r=.68; p<.0001) and placebo (r=.82; p<.0001) groups, despite the fact that the second assessment was collected one week after trial onset.

Conclusions: Relative to other imaging modalities, EEG-derived rACC activity represents a non-invasive and relatively easy to measure predictor of treatment outcome in depression. Such EEG measures could be integrated into clinical care in future mental health clinics to inform treatment decision-making.

Supported By: NIMH U01MH092221 and U01MH092250

Keywords: Anterior Cingulate Cortex, Prediction of Treatment Outcome, Antidepressant response, EEG

174. Administration of Selective Dietary Supplement in Early Postpartum is Associated with High Resilience against Depressed Mood: An Open-Label Trial

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Background: Postpartum depression (PPD) is the most common complication of childbearing with a 13% prevalence rate, but there are no widespread prevention strategies and no nutraceutical interventions have been developed. Postpartum blues (PPB) is often a prodromal state for PPD, since severe PPB strongly elevates risk for PPD. A dietary supplement kit consisting of monoamine precursor amino acids, tryptophan and tyrosine, and dietary antioxidants was created. The aim of this open-label study was to assess whether the dietary supplement reduces the vulnerability to depressed mood at day-5 postpartum, the typical peak of PPB.

Methods: 41 healthy day-5 postpartum women were recruited into 2 groups. Supplemented group (n=21) received the dietary supplement (2g tryptophan, 10g tyrosine, blueberry juice-extract), Control group (n=20) not receiving supplements. PPB severity was quantitated by the elevation in depressed mood on the visual analogue scale (VAS) and the profile of mood state (POMS) following the sad mood induction procedure (MIP).

Results: Univariate analysis of variance demonstrated a robust induction of depressed mood on the VAS in the controls but no effect in the supplement group following the sad MIP (F(1,39)= 88.33, p<.001; effect size 2.9). A similarly effect of group on change in POMS depression scores was observed (F(1,39)= 19.81, p<.001).

Conclusions: The dietary supplement designed to counter functions of elevated MAO-A activity virtually eliminated the vulnerability to depressed mood during the peak of PPB. This suggests that this nutraceutical intervention is a highly promising approach to target this prodromal state of PPD.

Supported By: We would like to acknowledge the CIHR, OMHF, and Canada Research Chair for their support.

Keywords: Postpartum Depression, Monoamines, Monoamine Oxidase-A, Antioxidants, Prodrome
175. Effects of the Nicotinic Partial Agonist Varenicline on Smoking Lapse in Smokers with and without Schizophrenia

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Background: Varenicline is currently the most effective smoking cessation aid that has been found to improve abstinence rates in patients with schizophrenia. Smokers with schizophrenia have high rates of smoking cessation failure, are more highly nicotine dependent and experience greater cognitive dysfunction during withdrawal. Thus the importance of determining an effective treatment to successfully maintain smoking abstinence and prevent smoking relapse is warranted.

Methods: Varenicline, a nicotinic partial agonist, was titrated up to 2mg/day over 4 days and continued for a total of 6 days using a randomized, double-blind, cross-over design in patients with schizophrenia (N=14) and healthy controls (N=14).

Results: We found that in the total sample (N=33), varenicline (versus placebo) had a small effect on time to lapse in both patient (Cohen’s d=0.35) and control groups (d=0.28), but that in a subset of smokers with heavy nicotine dependence (FTND6), the effect size for varenicline was significantly higher in patients with schizophrenia (d=0.48) compared to healthy controls (d=0.28).

Conclusions: Implications suggest an adjunctive treatment is necessary for smoking lapse prevention in patients with schizophrenia. Future studies may examine the use of brain stimulation such as repetitive transcranial magnetic stimulation combined with varenicline to increase ability to resist smoking in this vulnerable population.

Supported By: GRAND 2012 Award
Keywords: Schizophrenia, Cigarette Smoking, Varenicline, Smoking Lapse, Tobacco Use Disorder

176. The Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) on Smoking Behaviour and Cognition in Smokers with Schizophrenia versus Non-Psychiatric Control Smokers

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Background: Rates of tobacco smoking and smoking cessation failure in schizophrenia (SZ) are higher than the general population. While first-line cessation aids such as bupropion, varenicline, and nicotine replacement therapies have shown promise, better treatments are needed. Our preliminary studies have shown high frequency rTMS suppresses tobacco craving in smokers with SZ. As such, we sought to determine the effects of active versus placebo-sham rTMS on smoking behavior and cognition in smokers with and without SZ.

Methods: Fourteen smokers with SZ, and n=14 controls were studied at baseline (smoking satiated), after 16 hours of smoking abstinence and after reinstatement of smoking, using a 3-day human laboratory paradigm. 20 Hz active and sham rTMS treatments were administered bilaterally to the dorsolateral prefrontal cortex. Treatment conditions were counterbalanced across subjects. Outcomes included a cognitive battery, tobacco craving, and psychiatric symptoms.

Results: Overnight abstinence produced a significant increase in tobacco craving and withdrawal in both groups (p’s<0.05) and these effects were reversed with smoking reinstatement (p’s<0.05); however, active rTMS did not modify this pattern of results. Compared to sham, active rTMS had no significant effects on any cognitive outcomes.

Conclusions: Short-term high-frequency rTMS treatment did not modify smoking abstinence-induced changes in cognition and tobacco craving in smokers with SZ. Compared to our previous findings, which used a 1-week rTMS treatment paradigm, short-term administration of rTMS may not be sufficient to modify cognition, craving and withdrawal outcomes in smokers with SZ. Further research on effects of rTMS on smoking behaviours in SZ using longer-term treatments is warranted.

Supported By: Canadian Institutes of Health Research (CIHR) Operating Grant (MOP 115145), to Dr. George and a 2013 Brain and Behavior Research Young Investigator Award to Dr. Barr.
Keywords: Schizophrenia, Cigarette Smoking, Repetitive Transcranial Magnetic Stimulation, Tobacco Use Disorder, Neurocognition

177. Autism Behavior Inventory – A Novel Tool for Assessment of Changes in Core and Associated Symptoms of Autism Spectrum Disorder

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Background: There are lack of validated tools for measuring change in the core and associated symptoms of autism spectrum disorder (ASD). The Autism Behavior Inventory (ABI) is a novel, user-friendly tool designed to assess changes in core and associated symptoms of ASD in response to interventions. This abstract describes the development of the ABI tools and the first preliminary findings from its use in a clinical trial of an intervention for children with ASD.

Keywords: Autism Spectrum Disorder, Behavior Inventory, Intervention Evaluation, Clinical Trials

Supported By: NIMH R01 MH093625, NINDS R01 NS089083, Autism Speaks, Autism Society, Autism Science Foundation, the Office of Special Education Programs, and the University of Michigan
Keywords: Autism Spectrum Disorder, Behavior Inventory, Intervention Evaluation, Clinical Trials

Thursday Abstracts
Autism Spectrum Disorder (ASD). We present data from a validation study of the Autism Behavior Inventory (ABI), a 73-item online parent rating scale, which was designed to be used as an outcome measure in clinical trials for ASD.

Methods: In an 8-week non-interventional trial, parents of 144 individuals with a confirmed diagnosis of ASD (aged 6–64 years), and 41 typically developing individuals, completed the ABI and other behavior rating scales at each visit. Parents also reported on burden using the Zarit Caregiver Burden Interview (ZBI).

Results: ABI domains exhibited good test-retest reliability (ICC 0.85 to 0.95). Pre-specified construct validity hypotheses regarding relationships between ABI Core, Social Communication (SC), and Restrictive Repetitive Behavior (RRB) scores and other scales were met (ABI Core vs Social Responsiveness Scale-2 [SRS-2] Total r = 0.81, ABI SC vs SRS-2 Social Communication and Interaction r = 0.68, ABI RRB vs SRS-2 Repetitive Behavior r = 0.76 and Repetitive Behavior Scale-Revised [RBS-R] r = 0.77). ABI Core, SC, and RRB scores were able to detect improvements in severity based on category change in SRS-2 Total Score (within-group effect sizes [ES] 0.63, 0.48, and 0.43, respectively). ABI RRB was able to detect improvements in overall burden from ZBI and was more sensitive than the SRS-2 Repetitive Behavior Score (ES 0.58 vs 0.15).

Conclusions: The ABI demonstrates good reliability, validity and sensitivity to change, and appears ready for evaluation as an informant-reported measure in ASD treatment trials.

Supported By: Janssen Research & Development, LLC

Keywords: Autism Spectrum Disorder, Cognitive Neuroscience, Symptom Tracker, Web-based tool, Clinical trial

178. Response Inhibition in Youth Undergoing Intensive Treatment for Obsessive Compulsive Disorder

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Background: Response inhibition (RI), the ability to suppress contextually irrelevant behaviors, has been shown to be impaired in obsessive-compulsive disorder (OCD). RI may be relevant to exposure and response prevention (ERP): the ability to inhibit compulsions is required for fear extinction learning. This study examined the relationship between RI and ERP outcome in youth undergoing intensive OCD treatment.

Methods: Participants were 23 youth (mean = 11.8 years old) admitted to an intensive ERP-based OCD treatment program. Measures at admission and discharge included the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and mean reaction time (RT) and stop-signal reaction time (SSRT; time to inhibit motor response) on a stop-signal task (SST). Linear regression analyses controlling for admission CY-BOCS were used to determine whether baseline SSRT predicted post-treatment CY-BOCS, and whether SSRT change was associated with CY-BOCS change.

Results: CY-BOCS scores significantly improved from pre- to post-treatment (p < .000). Mean RT significantly improved (p = .01), but SSRT did not (p = .11). At admission, CY-BOCS scores were not significantly correlated with RT (p = .87) or SSRT (p = .97). Regression analyses indicated that baseline SSRT did not predict CY-BOCS change (p = .61), nor was SSRT change associated with CY-BOCS change (p = .10).

Conclusions: Baseline data supported globally impaired RI, as indicated by a higher SSRT than reported previously for healthy controls. Results indicated improvement in general RT, but not SSRT. RI impairment was not found to be directly related to OCD severity or ERP outcome. These findings support the idea that RI deficits may not be directly related to OCD severity but may be an abnormal trait marker.

Supported By: K23MH103617 (Conelea), K23MH100607 (McLaughlin)

Keywords: Obsessive Compulsive Disorder (OCD), Response inhibition, stop-signal task, children and adolescence, exposure with response prevention

179. Childhood Maltreatment Moderates Antidepressant Treatment Response for Self-Injury in Borderline Personality Disorder

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Columbia University

Background: Following reports of childhood maltreatment moderating antidepressant (AD) treatment response, we conducted a secondary data analysis examining the moderating effect of childhood abuse on self-injurious behavior (SIB) in a trial comparing AD and Dialectical Behavior Therapy (DBT) in patients with Borderline Personality Disorder (BPD).

Methods: 55 patients with BPD (85% with co-morbid Major Depression) with current suicidal ideation, a recent suicide attempt and/or non-suicidal self injury were randomized to AD treatment or DBT; completed one week of Ecological Momentary Assessment both before and after treatment. Six times daily participants were prompted to report self-injurious behaviors. Mixed effect logistic regression tested the difference between pre- and post-treatment likelihood of SIB, with childhood adversity measures moderating the effect of time point.

Results: In the AD group, for subjects with no history of childhood physical abuse, likelihood of SIB in an epoch declined from 4.7% to 1%; while for those with physical abuse, it increased from 3.2% to 7.5% (OR = 17.7, p < .001). Subjects with more emotional, physical and sexual abuse, and emotional neglect benefited less from AD treatment. In the DBT group, likelihood of SIB declined from 5.6% to 1.9% regardless of physical abuse history.

Conclusions: These results extend previous findings that patients who report childhood abuse do not benefit from AD to the same extent as those who do not, to BPD. For psychotherapies like DBT, the moderating effect likely does...
not apply, indicating a separate biological subtype for abused patients, perhaps characterized by stress sensitivity, changed brain morphometry and immune and metabolic abnormalities.

Supported By: 1R01 MH61017; 1R01MH109326; 4P50MH090964

Keywords: Antidepressant, ecological momentary assessment, self-harm, DBT, abuse

180. Clinical and Functional Imaging Correlates of Rumination and Obsessiallity in Anorexia Nervosa

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Background: Cognitive rigidity has long been observed in AN, and both obsessiallity and rumination have been proposed as contributing processes. Neural systems thought to underlie these processes include the mesocortical system (MCS) and the default mode network (DMN), respectively. We investigated whether these constructs change with weight restoration, whether they are associated with prognosis, and the underlying neural correlates.

Methods: Hospitalized females with AN (n=22), ages 16-25 years, and matched healthy controls (HC, n=23) were administered the Obsessive-Compulsive Inventory-Revised (OCI-R) and the Ruminative Responses Scale (RRS) and completed resting state fMRI pre- and post-treatment for AN (HC were scanned twice). Among AN, weight was assessed over four weeks after hospital discharge.

Results: OCI-R and RRS were significantly higher among AN compared with HC (ps<0.0001), with no significant change with weight restoration (df=2.34, p=0.13; df=0.89, p=0.60, respectively). OCI-R after treatment, change in OCI-R, and change in the brooding subscale of treatment were associated with weight slope after discharge (r=−0.45, p=0.04; r=−0.44, p=0.05; r=−0.05, p=0.02, respectively). AN, compared with HC, showed decreased connectivity within the DMN at T1; no group differences in DMN connectivity were detected at T2. Decreased DMN connectivity between the right lateral parietal cortex (RLP) and posterior cingulate cortex (PCC) was associated with increased brooding at T1 among AN (r=−0.46, p=0.03). There were no differences in functional connectivity within the MCS at either time point.

Conclusions: Obsessionallity and rumination may relate to longer-term prognosis of AN, with neural correlates in the DMN but not the MCS.

Supported By: R21 MH099388

Keywords: Resting state functional connectivity, Anorexia Nervosa, Rumination

181. Trait Rumination Moderates the Association between Ventrall Striatum Activity during Anticipation and Outcome of Monetary Reward

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Background: A typical phenomenon in depression is the tendency for ruminative thinking, a persistent thought pattern revolving around self-referential negative affect. Another consistent finding in depression is aberrant ventral striatal (VS) activity when anticipating and receiving rewards. A tendency for negative self-referential thought may influence how external rewards are anticipated and processed. However, to date, no study examined the neural link between rumination and VS activity during reward-related processing. This study aimed at exploring this link using functional magnetic resonance imaging (fMRI) in healthy and depressed participants with different levels of trait rumination.

Methods: We scanned a sample composed of 51 healthy participants and 17 participants diagnosed with major depressive disorder while performing a gambling task that includes an anticipatory phase prior to receiving an uncertain monetary reward or loss outcome. Participants also completed the Beck Depression Inventory (BDI) and the Ruminative Response Scale (RRS) assessing trait depression and rumination, respectively.

Results: Across the sample, RRS scores correlated negatively with VS activity during outcome anticipation. This correlation remained significant even after controlling for BDI scores, suggesting its specificity to rumination. Furthermore, a hierarchical multiple regression analysis showed that RRS scores moderated the association between VS activity during outcome anticipation and, specifically, reward outcome processing, even after controlling for demographic variables and depression symptom severity.

Conclusions: Our results suggest a link between negative, self-referential thought tendencies and processing of external rewards. These findings may contribute to elucidating the association between depression, rumination, and aberrant reward-related processes.

Supported By: Israeli Ministry of industry

Keywords: Rumination, Depression, Ventrall Striatum, Reward network, Nucleus Accumbens

182. Increased Executive Functioning and Suicide Attempts in Depressed Adolescents with Bipolar Disorder

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Background: Bipolar disorder (BD) is associated with a significant risk for suicide. Previous studies of adults with
BD have demonstrated a relationship between deficits in executive function and increased suicidality. This relationship has not yet been investigated in bipolar youth. The present study examined the association between a history of suicide attempts and executive functioning in youth with BD.

Methods: Twenty depressed bipolar participants, ages 13 to 21, completed a diagnostic interview, mood, and executive function measures. All participants were given the WCST, Trail Making Test, Color-Word Interference Test to create an executive function composite score, and the Columbia Suicide Severity Rating Scale to assess lifetime symptoms of suicidal ideation and behavior.

Results: All participants had a history of suicidal ideation and 15 participants had a history of attempts. Logistic regression was performed on suicidal behavior with executive functioning, age, and depression scores as predictors, $X^2 (3, 20) = 12.88, p = .005$. Executive function predicted the occurrence of suicide attempts in bipolar youth, $X^2 (1, 20) = 3.90, p < .05$. Specifically, better executive performance was associated with a history of suicide attempts.

Conclusions: Bipolar adolescents with a history of suicide attempts demonstrated better performance on tests of executive function. These findings were surprising and differ from previous reports in suicidal adults. The relationship between executive function and suicide-risk in bipolar youth may be impacted by brain development during adolescence. Additional studies are needed to examine the interaction between neurodevelopmental changes in executive functioning and suicide-risk in bipolar youth.

Supported By: Utah Science Technology and Research (USTAR) initiative at the University of Utah

Keywords: Bipolar Disorder, Executive Function, Suicide Attempts, Suicidality, Adolescents


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Background: Few studies have investigated the effect of lithium treatment on cognitive function that is weighed against its prophylactic efficacy. The aim is to delineate the causal relationship among cognition, clinical symptoms, medications, demographic variables, the response to lithium and, as a dependent variable, functional outcome in lithium-treated euthymic patients with bipolar disorder.

Methods: Ninety-two lithium-treated bipolar patient and 196 age- and sex-matched healthy controls were evaluated by the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS). The patients were also assessed by the Social Functioning Scale (SFS) and were dichotomized by “The Retrospective Criteria of Long-Term Treatment Response to lithium in Research Subjects”.

Results: The Structural Equation Modeling (SEM) revealed that the lesser number of mood episodes, lower age and higher premorbid IQ predicted the better performance on BACS composite score, while the lesser negative symptoms, better performance on BACS composite score and lower dosages of the first generation antipsychotics predicted the higher total SFS score. Although the high lithium responders outperformed the cognitive subdomains reflecting processing speed, and had the lesser negative symptoms, lesser number of mood episodes and higher total SFS scores, relative to the low lithium responders, when unadjusted for other covariates, the SEM showed that the response to lithium was associated to the negative symptoms and number of mood episodes solely.

Conclusions: These results suggest that the SEM delineates how the demographic and clinical variables, cognition, and the response to lithium treatment are causally associated and converge on the social function.

Keywords: Bipolar disorder, Cognitive function, Social function, Lithium responder, BACS, SFS

184. Effects of Early and Adult Stress on Symptom Severity and Neurocognitive Function of Major Depression

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Background: Both childhood abuse and stressful life events (SLE) preceding the onset of symptoms have been associated with major depression (MD). However, little is known about how these stressors affect neurocognitive function in MD patients. The present study extends the literature by examining the effects of childhood abuse and SLE previous to the first episode of MD, assessing both mood and neurocognitive symptoms.

Methods: 88 patients (Age=51.24, 63.6% females) were assessed for depressive symptoms severity (HDRS-17), childhood abuse (Childhood Trauma Questionnaire; emotional, physical and sexual abuse subscales), adult SLE (St Paul Ramsey Life Experience Scale) and neurocognitive function (combined T scores of DSST and RAVLT -learning and memory). Two independent linear regressions were analyzed, with neurocognitive and symptoms severity as dependent variables and demographic, clinical and stress scales as independent ones.

Results: Adult SLE ($β$= .321; $p=0.001$) and HDRS-17 ($β$= .519, $p<0.001$) were significantly associated with neurocognitive function ($R^2=.434; F(2, 70)=26.064; p<.001$). In contrast, years of schooling ($β$= −.286; $p=0.006$) and the childhood emotional abuse subscale ($β$=−.256; $p=0.013$) were associated with symptoms severity ($R^2=.139; F(2, 87)=6.864; p=0.002$).

Conclusions: Current study corroborates the negative impact of mood on neurocognition. But as far as we know, is the first one showing how an SLE preceding illness onset impacts on patients’ cognition. While stress during adulthood influences neurocognition, early emotional abuse and years of schooling impact on symptoms severity, suggesting that stressful events
may have different impacts on MD depending on the stage of life in which patients are exposed.

**Keywords:** Neurocognitive outcome, Early Life Stress, Unipolar Major Depression

185. Engagement in a Visual Task Increases Postural Stability in Veterans with Mild Traumatic Brain Injury

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**Background:** Patients with mild traumatic brain injury (mTBI) often complain of balance problems. Balance is the ability to remain upright and steady with minimal postural sway, or horizontal movement of the center of gravity. Postural sway problems can indicate neurological dysfunction in sensory integration and motor coordination.

**Methods:** Nineteen veterans with history of mTBI (mean age 49.5±11.4 years) and 26 controls (no TBI history; 49.6±12.1 years) were assessed. Participants stood with feet together on a Wii balance board for 60 seconds with eyes: 1) closed, 2) open, or 3) open, searching a paragraph of text attached to the wall for a particular letter ("search" task). Sway was quantified as the distance traveled per second in two directions: anterior-posterior (AP) and medial-lateral (ML).

**Results:** A group (mTBI, control) x task (eyes closed, eyes open, search) mixed model ANOVA showed a significant main effect of task compared to the eyes open condition only in the mTBI tests revealed significant main effect of task compared to the eyes open condition only in the mTBI group. For ML sway, there was a significant main effect of task (increased sway in the eyes closed task compared to the other tasks), but not group.

**Conclusions:** Engagement in a visual task benefitted mTBI participants’ postural stability. This task engagement may add visual input to enhance integration of visual, vestibular, and proprioceptive information in mTBI to increase postural stability. Current findings suggest that objective assessment of postural sway may be an important tool in guiding rehabilitation of veterans with mTBI.

**Supported By:** Defense and Veterans Brain Injury Center

**Keywords:** Mild Traumatic Brain Injury, Veterans, Balance, Postural Sway, visual

186. Compensatory Brain Network Mechanisms Underlying Calculation Difficulties Characteristic of Dyscalculia

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**Background:** Understanding how the brain compensates for dysfunction may provide new therapeutic avenues for exploration. Here, we examine potential compensatory mechanisms engaged in dysfunctional parietal cortex activation, underlying calculation difficulties typical of dyscalculia.

**Methods:** Subjects performed a series of event-related working memory (WM) calculation and maintenance tasks while in a 3T GE MRI scanner. We first examined 34 healthy individuals with poor calculation accuracies in WM (<50%) but with preserved WM maintenance (>80%), relative to 34 controls (>80%), to define inferior parietal sulcus (IPS) regions engaged in WM calculation. We next examined 100 healthy subjects with high performance accuracy (>80%) during WM calculation, yet varying IPS engagement. Subjects with relatively reduced IPS activation may engage compensatory circuitry to maintain performance. SPM12 was used in fMRI data processing and dynamic causal modeling.

**Results:** For WM calculation dysfunction, we found relatively reduced IPS engagement (48,-44,50, t=4.18, p<0.001), associated with relatively increased effective connectivity from IPS to angular gyrus, and IPS to striatum (p<0.01). On the other hand, similarly low IPS engagement but without performance deficits was associated with relatively increased engagement of the angular gyrus (40,-58,28, t>3.8, p<0.001), with relatively increased effective connectivity from angular gyrus to IPS, and striatum to IPS (p<0.05)—an apparent reversal of the dysfunctional connectivity relationships.

**Conclusions:** Enhanced angular gyral and striatal connectivity to the IPS may compensate for relative IPS dysfunction. These network relationships may be implicated in mitigating effects of dyscalculia through alternative problem-solving and information processing strategies.

**Supported By:** Lieber Institute for Brain Development

**Keywords:** Dyscalculia, Dynamic causal modeling, Brain networks, Inferior parietal, Angular gyrus

187. Differential Predictors of Stress Resilience during Working Memory across Urban and Rural Upbringing

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**Background:** Resilience, or “bouncing back” in the face of adversity and stress, may mitigate risks for neuropsychiatric disorders. Here, we examined the effects of social stress on working memory (WM), hypothesizing that performance resilience under stress and accompanying neural correlates may be differentially influenced in urban versus rural upbringing. Specifically, urban upbringing may be associated with relatively...
higher childhood socioeconomic indicators, but less play and other non-socioeconomic effects, which may differentially influence brain functioning.

Methods: One hundred sixty-five adult subjects currently living in Beijing, China with either rural (n = 89) or urban (n = 76) upbringing but similar current socioeconomic status were scanned in a 3T GE MRI. Subjects performed a WM computation task, with or without induced social stress featuring a competitor appearing to score better. Detailed life trajectory information was also obtained for all subjects.

Results: Parental education predicted resilient WM computation performance under stress in individuals with urban upbringing (p < 0.04), accompanied by a modulation of a stress-induced reduction of inferior prefrontal engagement (p < 0.001 uncorrected). On the other hand, play and social relationships, but not socioeconomic factors, appeared to be associated with resilient WM computation performance under stress individuals with rural upbringing (p < 0.01), accompanied by a modulation of stress-induced reduction of posterior cingulate engagement during WM computation (p < 0.001 uncorrected).

Conclusions: Dissociable childhood socioeconomic and non-socioeconomic factors influence adaptive stress responses at differing lateral prefrontal and medial cortical brain regions in individuals with urban versus rural upbringing.

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Keywords: Cognitive resilience, Working memory, social stress

188. Effect of Stress on Prefrontal Network Effective Connectivity during Working Memory Computation

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Background: Working memory (WM) impairment is a key feature of several neuropsychiatric disorders, including schizophrenia. Stress is also known to affect working memory function, as well as neuropsychiatric disorders. Here, we examined multi-regional effective connectivity networks during WM computation with varying levels of social stress. We hypothesized that social stress would decrease effective network connectivity.

Methods: We studied 40 adult subjects scanned in a 3T-MRI as they performed a WM task that included computation of numerical information. Social competitive stress was induced in half of the blocks by pairing the subject against a competitor that performed better. Imaging analysis was carried out using SPM12, Dynamic Casual Modeling, and the Brain Connectivity Toolbox.

Results: Subjects robustly engaged prefrontal, parietal, and subcortical brain regions in WM computation (p < 0.05 FWE corrected). Stress was associated with relatively reduced engagement of prefrontal, parietal and striatal regions (t = 4, p = 0.001 uncorrected). Effective connectivity networks that recruited the dorsolateral prefrontal cortex, parietal cortex, insula, striatum, medial frontal cortex, fusiform gyrus, and angular gyrus showed reductions in dorsolateral prefrontal control of the parietal cortex under stress (p < 0.005). Network level effective connectivity strength from the dorsolateral prefrontal cortex to all other nodes of the WM network was also reduced under stress (p < 0.05), as well as input from all other nodes to the parietal cortex (p < 0.05).

Conclusions: Our results suggest that the social stress induced in our paradigm reduces dorsolateral control of parietal and other regional brain interactions during WM computation.

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Keywords: Effective connectivity, Working memory, Social stress, Dynamical Causal Modeling, Neuroimaging
190. Social Cognition in Early Schizophrenia: Exploratory Factor Analysis and Subcortical Biomarkers

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**Background:** One of the central determinants of functional outcome in schizophrenia is social cognition (SC). With the wide array of SC domains, factor-analysis provides a powerful tool to identify commonalities amongst their underlying dysfunctions and its neural underpinnings.

**Methods:** The present study performed exploratory factor analysis (EFA) on 90 patients with early course schizophrenia using seven validated SC subtests. Subsequent shape analyses of the amygdala and hippocampus were performed using the MAGeT Brain pipeline to investigate their relationship to the composite scores derived from SC factors.

**Results:** EFA revealed a 3-factor solution, representing the domains of emotion management, emotion recognition, and theory of mind-emotion context processing, together accounting for 63.58% of the variance. The surface area of the right amygdala was identified to be positively correlated with the emotion recognition factor (p<0.05, FDR corrected), while the left hippocampus, specifically the surface area of the subiculum, was identified to be associated with the theory of mind factor (p<0.05, FDR corrected).

**Conclusions:** Our EFA indicates overlap amongst SC subtests which surmount to represent three different SC domains. Furthermore, shape analysis reveals that surface area of the amygdala and hippocampus play a supportive role in emotion recognition and theory of mind factors respectively. In the future, amygdala and hippocampus play a supportive role in emotion management.

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**Keywords:** Schizophrenia, Working Memory, Human Connectome Project, Dynamical Causal Modeling, Activation


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**Background:** Persons exhibiting clinical high-risk (CHR) symptoms similar to but less severe than those of schizophrenia have an elevated risk of developing this disorder. We sought evidence that CHR patients have deficits in processing relationships between meaningful stimuli, similar to abnormalities previously found to be associated with schizophrenia. We used the N400 event-related potential (ERP) waveform as a neurophysiological probe of activation of concepts in semantic memory. We hypothesized that CHR patients would exhibit larger (more negative) than normal N400 amplitudes in response to stimuli meaningfully related to a preceding prime stimulus - reflecting deficient semantic priming (activation of related concepts).

**Methods:** We recorded ERPs in 8 CHR patients and 8 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 via button-press whether or not the target was a word.

**Results:** Across groups and SOAs, N400 amplitudes were larger (more negative) for unrelated than related targets (p=0.02). However, this semantic priming effect was smaller in patients than controls at the 750-ms SOA (p<0.05).

**Conclusions:** The results suggest N400 semantic priming is deficient early in the psychotic disease process, at least at relatively long intervals after prime stimuli. This abnormality may represent an early biomarker of the psychotic process.

**Supported By:** Ontario Mental Health Foundation; Ontario Ministry of Health and Long-Term Care (AHSC AFP Innovation Fund)

**Keywords:** Schizophrenia Spectrum, Prodrome, SEMANTIC ASSOCIATION, Event-related Potentials, delusions

192. Effect of Varenicline Doses and Plasma Levels on Cognitive Function in Non-Smokers with Schizophrenia

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**Background:** Schizophrenia (SZ) is associated with both high rates of tobacco smoking and pervasive cognitive deficits that may be linked to dysregulation of nicotinic acetylcholine receptors (nAChRs). Effective treatments for cognitive deficits among SZ patients remain an unmet need. The nAChR partial agonist varenicline has been shown to have cognitive enhancing effects in SZ smokers; however non-smokers have been poorly studied. Therefore, we studied dose-dependent effects of varenicline in SZ and control non-smokers on several cognitive outcomes.

**Methods:** Varenicline (0, 1, 2 mg/day) was administered over 3 days with a 1-week washout period between test weeks, in biochemically verified non-smoking SZ patients (n=15) and controls (n=15). Varenicline plasma levels were collected on...
Day-3PM and effects on cognitive outcomes including visuospatial working-memory (VSWM) and verbal memory were evaluated.

**Results:** At baseline, controls performed better on several cognitive outcomes than SZ (p<0.001). Patients appeared to perform better on 1mg/day in contrast to controls on 2mg/day. Correlation analyses between plasma varenicline levels and VSWM performance revealed improved VSWM performance with increased plasma levels among SZ patients in 1mg/day condition (p<0.08). For controls, plasma levels were positively related to VSWM (p=0.013) and verbal memory (p=0.005) performance in the 2mg/day condition. There were no significant effects of varenicline on psychotic or depressive symptoms.

**Conclusions:** Patients on 1mg/day condition and controls on 2mg/day condition had better cognitive performance with increasing plasma levels. Larger studies with longer duration of varenicline treatment are warranted to parse the relationships between varenicline, plasma levels and cognition in non-smokers with SZ.

**Supported By:** Institute of Medical Sciences Graduate Fellowship from the University of Toronto; Investigator-initiated grant from Pfizer, Inc. (WI171136); CIHR Operating Grant MOP115145 (to Dr. George).

**Keywords:** Schizophrenia, Non-Smokers, Varenicline, Cognition, Visuospatial Working Memory

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**193. Emitted P3a and P3b in Chronic Schizophrenia and in First-Episode Schizophrenia-Spectrum Psychosis**

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**Background:** The P3 is biphasic, with P3a reflecting automatic orienting and P3b cognitive processing. Reductions in P3b in first episode schizophrenia-spectrum individuals (FE) are present on target detection “oddball” tasks, although P3a reductions are equivocal. P3 can also be “emitted” by an expected but missing stimulus. Surprisingly, the emitted P3 has been little studied in long-term schizophrenia (Sz) and not at all in FE.

**Methods:** Twenty-seven Sz (minimum 5 years diagnosis) were compared to 20 matched controls (HCSz), and 27 FE (within 6 months of their first psychotic episode) were compared to 26 matched controls (HCFE). Participants were presented with standard sets of four identical tones (1kHz, 50ms, 330ms SOA, 750ms ITI). For one in seven sets, the fourth tone was missing. Participants counted the number of tones within each set, with no instruction to detect missing tones.

**Results:** The P3b emitted by missing tones was significantly reduced in both Sz and FE (p=.039 and p=.017, respectively).

**Conclusions:** Sz and FE displayed impaired emitted P3b on a missing tone task. Presumably, HC implicitly developed an expectation for groups of 4 tones, with the P3b emitted when the 4th tone was missing. By contrast, Sz and FE did not. The emitted P3b may be useful to understand cognitive neuropathophysiology early in psychosis. Its reduction in FE suggests it may show promise as a biomarker of schizophrenia presence. Future work will assess its sensitivity to the schizophrenia prodrome prior to conversion to frank psychosis among clinical high risk individuals.

**Supported By:** NIH R01 MH094328

**Keywords:** First-Episode Psychosis (FEP), Schizophrenia, P300

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**194. Exploring Neural Basis of Emotional Cognition Using Fear Conditioning by Interpersonal Conflicts in Patients with Schizophrenia**

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**Background:** Emotional cognition has been an important area of research in schizophrenia. Simple aversive stimuli conventionally used in previous conditioning paradigm such as electric shock have a weakness of not representing real-world conflicts that seriously involve social context. We recently developed an interpersonal stimulus to reflect such a social context, and it has successfully been applied to healthy individuals (Tada et al. Plos One, 2015). The objective of this study was to explore neural basis of emotional cognition in schizophrenia by measuring autonomic response using skin conductance response (SCR) to the interpersonal stimuli.

**Methods:** Eighteen female patients with schizophrenia (ICD-10) underwent two types of fear conditioning experiments of an aversive sound, and an interpersonal stimulus with a picture of actors’ faces with recorded unpleasant verbal messages. The paradigm consisted of three consecutive phases: habituation, acquisition, and extinction. Conditioned response was quantified by differential SCR between stimuli paired with (CS+) and unpaired with (CS-) conditioned stimuli (US) using paired t-tests during the acquisition, early and late extinction phases.

**Results:** Fourteen subjects with evaluable SCRs to the CS+ during the acquisition phase to either of two stimuli were included in the analysis. No statistically significant differences in SCRs were observed between CS+ and CS- in both acquisition and extinction phases, regardless of the types of stimuli.

**Conclusions:** Female patients with schizophrenia failed to get conditioned with the interpersonal stimuli or the aversive sound, which suggests their qualitative difference in emotional processing from healthy individuals.

**Supported By:** Inokashira Hospital Grants for Psychiatry Research; Lilly Grant

**Keywords:** emotional cognition, fear conditioning, interpersonal conflicts, skin conductance, schizophrenia
195. Increased Dopamine Synthesis Capacity in Gambling Addiction Predicts Drug-Induced Enhances in Reward Learning

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Background: The dopamine hypothesis of gambling addiction is pervasive. Moreover, pathological gamblers respond abnormally to dopaminergic drugs. However, there is little to no direct evidence for a categorical difference between pathological gamblers and controls in terms of dopamine transmission at baseline. Multiple attempts to provide evidence for the hypothesis that pathological gambling (PG) as in the case of drug addiction, is accompanied by low dopamine D2-family receptor availability relative to controls, have failed. Here we provide direct evidence for the dopamine hypothesis of PG by focusing on a different aspect of dopamine transmission: synthesis capacity.

Methods: We assessed dopamine synthesis capacity with PET 6-[18F]fluoro-L-DOPA dynamic scans in 15 controls and 13 pathological gamblers and investigated whether differences in dopamine synthesis capacity between gamblers and controls can account for their differential cognitive response to dopaminergic drug administration.

Results: Dopamine synthesis capacity in the striatum was enhanced in pathological gamblers compared with controls. Furthermore, this enhanced dopamine synthesis capacity predicted the effect of the D2 receptor antagonist sulpiride (400mg oral) on reward (versus punishment) learning. Across groups, individuals with high dopamine synthesis capacity exhibited drug-induced enhancement of reward learning, while individuals with low synthesis capacity exhibited attenuation of reward learning.

Conclusions: These data provide strong empirical evidence for the pervasive but hitherto unsupported dopamine hypothesis of gambling addiction. They also reinforce the baseline-dependency principle of dopaminergic drug effects, thus demonstrating the importance of a dimensional as opposed to a categorical approach to dopaminergic treatment in psychiatry.

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Keywords: Dopamine, Pathological gambling, Reinforcement learning, PET imaging, Individual differences

196. The Neural Correlates of Compulsive Alcohol Seeking

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Background: A hallmark of alcohol addiction is continued alcohol seeking despite adverse consequences. Animal models have identified the medial prefrontal cortex and insula as key regions for compulsive alcohol seeking (Seif et al., 2013). Despite the importance of compulsivity in addiction, there have been few human studies investigating this phenomenon. Here, we translate a preclinical paradigm to investigate the neural substrates of compulsive alcohol seeking in human participants.

Methods: Light drinkers (LDs; n=13) and heavy drinkers (HDs; n=9) participated in the study. Imaging was performed on a 3T scanner. Participants completed an fMRI paradigm that measured willingness to obtain alcohol points at different threat levels. Imaging results were analyzed using AFNI (Cox, 1996). A GLM was used to analyze cue and feedback periods at each threat level.

Results: HDs attempted to earn more alcohol points under high threat than LDs (t = 2.8, p = 0.01). There were no group differences in low threat or safe alcohol conditions. During high threat alcohol cue presentation, HDs showed increased BOLD activation of the vmPFC (xyz = 2.37,-1; t = 4.8, p < 0.005), relative to LDs.

Conclusions: We have developed a translational paradigm to investigate alcohol-related compulsivity in a clinically relevant population. We found that HDs were willing to risk an adverse consequence to earn alcohol. During high threat alcohol cue presentation, HDs displayed increased vmPFC activation, a region associated with aversion resistant alcohol seeking in preclinical models. This finding suggests a potential neural substrate for compulsive alcohol seeking in heavy drinkers.

Supported By: NIH NIAAA IRP

Keywords: Alcohol Dependence, Compulsivity, fMRI, Translational research

197. Antipsychotic Drug Precipitated Primary Parkinson’s: A Case Report

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Background: Drug-induced Parkinsonism differs from Primary Parkinson’s clinically and at molecular level. It is, therefore, unlikely that antipsychotics can precipitate Primary Parkinson’s. A case is presented with late-onset psychosis with no features of Parkinson’s prior to onset of psychosis who developed Primary Parkinson’s after Risperidone.

Methods: A 59 year old female with recent-onset schizophrenia was brought to emergency. She had no history of any past medical illness except a hereditary skin condition. She was initiated on Risperidone (8mg). Thereafter, there was development of back
stiffness and slowness in movements, along with depression. On examination, mild rigidity in bilateral elbow (L>R), along with masked facies was seen. With an impression of drug-induced Parkinsonism, she was started on Trihexyphenidyl along with an antidepressant but parkinsonian features persisted. MRI Brain showed white-matter hyperintensities in external capsule alongside some non-specific changes. Risperidone was tapered off and Aripiprazole (5mg) started, watching for re-emergence of psychosis. Parkinsonian symptoms still persisted. TroDAT scan showed presynaptic dopaminergic dysfunction (L>R) indicating Primary Parkinson’s. She was started on Levodopa+Carbidopa combination. Parkinsonian symptoms improved while psychosis didn’t re-emerge.

Results: Since the present case had no parkinsonian features before the onset of psychosis, diagnosis of drug-induced parkinsonism was entertained. Non-resolution of symptoms on stopping antipsychotics raised the possibility of protracted side-effects. Non-improvement with anticholinergics and significant MRI findings called for TroDAT scan, which identified Primary Parkinson’s which apparently manifested after starting Risperidone.

Conclusions: Although adequate literature exists on drug-induced Parkinson’s, inadequate literature is present on drug-precipitated Parkinson’s. Although the association of usage of antipsychotics and Primary Parkinson’s is temporally correlated, it needs further investigation.

Keywords: Antipsychotics, Parkinson's disease, side effects

198. Skeletal Effects of Depression and SSRIs
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Background: Preclinical and clinical studies suggest that selective serotonin reuptake inhibitors (SSRIs) impair bone metabolism, reducing bone mass and increasing bone fracture. However, prospective studies examining this concern in youths have not been conducted.

Methods: Fifteen to 20 year-old unmedicated participants or within a month of starting SSRI therapy were enrolled in a longitudinal study examining the skeletal effects of SSRIs. Every eight months, anthropometric measures were obtained following standard procedures and dual-energy x-ray absorptiometry was used to measure body composition. Sex-age-ethnicity-height-specific Z-scores were generated, using published normative data. The clinical assessment battery included the Longitudinal Interview Follow-up Evaluation for Adolescents (A-LIFE) and a DSM-IV-TR diagnosis incorporating information from the review of medical records and the self- and researcher-completed symptom rating scales, the NIMH Diagnostic Interview Schedule for Children IV, and an unstructured interview by a child psychiatrist. Mixed regression analysis examined predictors of longitudinal change in total body less head bone mineral content (BMC).

Results: A total of 259 participants (60% females, mean age: 18.9±1.6 years) were followed for an average 1.5±0.8 years. At study entry, 47% were taking an SSRI. After adjusting for age, sex, physical activity, vitamin D concentration, and time, markers of depression were inversely associated with BMC, while markers of generalized anxiety disorder were associated with increased BMC. Cumulative exposure to SSRIs was not significantly associated with change in bone mass.

Conclusions: In this longitudinal study, depression but not exposure to SSRIs was associated with reduced bone mass while generalized anxiety disorder was associated with increased bone mass.

Supported By: R01MH090072
Keywords: Adolescent Depression, Antidepressants, Selective Serotonin Reuptake Inhibitors, Bone Mass

199. Associations between Specific Dissociative Symptoms and Symptom Subsets and Anti-Depressant Response to Ketamine
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Background: Ketamine has been shown to produce rapid antidepressant effects in major depression and bipolar disorder. Due to ketamine’s glutamatergic properties, many patients report dissociative effects, which recent studies have shown to be associated with increased anti-depressant response. Thus we investigated the connection between distinct subscales of dissociation and differing treatment response.

Methods: Data from 126 treatment-resistant depression patients (MDD=84, BP=42), who received a single-dose subanesthetic infusion of ketamine over a 40 minute period (0.5 mg/kg) were evaluated. Dissociative effects were measured using the Clinician-Administered Dissociative States Scale (CADSS) at baseline and at 40 minutes post-infusion. Derealization, depersonalization, amnesia subscales, and a total score were used to examine ketamine’s antidepressant response, measured with the Hamilton Depression Rating Scale (HDRS-17) at 230 minutes post-infusion, day 1, and day 7.

Results: An increase in derealization was significantly correlated with decreased HDRS-17 scores at 230 minutes (r=−0.19, p=0.04), depersonalization at day 7 (r=−0.24, p=0.047), as well as some CADSS individual items at various time intervals (p <0.05). The change in CADSS total score was also related to decreased HDRS-17 scores at 230 minutes (r=−0.21, p=0.02) and at day 7 (r=−0.23, p=0.050).

Conclusions: The findings of the current study suggest that subscales of dissociation, specifically derealization and depersonalization, may be associated with antidepressant response. Further, individual dissociative items and the CADSS total score were also related to greater improvements in depression scores post ketamine infusion. Future research should explore whether derealization and depersonalization, but not amnesia symptoms, share a related mechanism to antidepressant response.

Supported By: NIMH
Keywords: ketamine, dissociation, depression
200. Effects of Medications on RNA-Seq Gene Expression from Anterior Cingulate Cortex in Adult Major Psychiatric Disorders

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Background: Medications potentially may have a profound effect on gene expression in human brain. To study the molecular characteristics of psychiatric conditions in postmortem tissue, medication history must be taken into account. In this study, blood toxicology screens at the time of death were used to assess effects of medication on RNA expression in postmortem brain of patients with major psychiatric disorders.

Methods: Blood toxicology of over three hundred drug compounds and metabolites across diagnostic groups was obtained. We selected 44 antipsychotic positive (11 BP, 5 MD, 28 SZ) and 43 antidepressant positive (19 BP, 14 MD, 10 SZ) cases based on toxicology results and compared them to the 61 medication negative subjects. To analyze the effects of medication on RNA-seq gene expression data in the subgenual anterior cingulate cortex, we used the GLM model that included RNA Integrity Number (RIN), Age, Sex, Race, Batch and Toxicology Result.

Results: When comparing antidepressant positive with antidepressant negative subjects, we found 56 genes significant at FDR<.05. In the antipsychotic dichotomy 68 genes were significant at FDR<.05. NR4A1 was significantly different in the antipsychotic positive group, at FDR=1.6e-4. NR4A1 expression has been known to be affected by antipsychotics.

Conclusions: Our results indicate that the presence of psychiatric therapeutics should be taken into account in the analyses of molecular data.

Keywords: RNA-seq, Toxicology, Postmortem, Schizophrenia, Mood Disorders

201. Measuring Dissociative Effects of NMDA Receptor Antagonists in the Treatment of Depression

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Background: The discovery of ketamine’s ability to rapidly induce antidepressant effects in a substantial proportion of previously treatment non-responsive patients has offered hope to patients, clinicians, and drug developers alike. Yet, concerns remain related to the dissociative effects commonly associated with this class of NMDA receptor antagonist drugs. Most trials involving these novel therapeutic agents have used the Clinician Administered Dissociative States Scale (CADSS) to assess the dissociative effects of the treatments. However, there is a growing question as to how well this scale is capturing the patients’/subjects’ experiences with these drugs. We will discuss the findings of a study examining the changes in the CADSS rating scale associated with NMDA receptor antagonist treatment of depression.

Methods: Changes in the CADSS associated with ketamine treatment over several studies were analyzed to examine specific clusters of change and temporal patterns. A subgroup of patients treated with ketamine for major depressive episodes were also interviewed to collect qualitative data regarding the experience.

Results: As expected CADSS scores did show significant but highly variable transient changes following drug administration. The magnitude of the effects decreased with repeated exposure. However, qualitative interviews suggest the scale does not accurately capture the changes in dissociative-like symptoms that are experienced by many of the patients.

Conclusions: New scales specifically designed to assess drug related changes in cognitive and dissociative symptoms could help to better track and understand the effects of these novel treatments on these domains, and possibly be used to evaluate the relationship between these effects and clinical outcome.

Keywords: Ketamine, NMDA antagonists, dissociation, Rating scales, antidepressant trial

202. Agreement Between Knowledgeable Clinicians and Expert Consensus Criteria in Diagnosing Neuroleptic Malignant Syndrome

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Background: Effective management of neuroleptic malignant syndrome (NMS) requires prompt recognition because it can emerge suddenly and is potentially fatal, but there are no established diagnostic criteria. This study is the first to validate recently published international expert consensus (IEC) criteria for diagnosing NMS, which assign priority points to each element based on its relative diagnostic importance.

Methods: Archived reports of clinician-initiated contacts with a national NMS telephone consultation service corresponding to 12 years of operation were reviewed to identify possible NMS cases based on explicit inclusion criteria (n=221). The performance of the IEC criteria was evaluated with respect to two diagnostic reference standards: DSM-IV-TR research criteria and telephone consultant clinical diagnoses. Receiver operating characteristic (ROC) curve analysis was used to determine the IEC priority point cutoff score associated with optimal sensitivity and specificity.

Results: Area under the ROC curve (AUC) was greatest for slightly modified (less stringent) DSM-IV-TR criteria (.857, p<.001), and least for consultant diagnoses (.715, p<.001). The highest level of agreement (kappa coefficient) was observed for a cutoff score of 74 and the less stringent DSM-IV-TR criteria; this cutoff demonstrated the highest agreement across all classifications.
Conclusions: An IEC priority point cutoff score of 74 provided the optimal diagnostic threshold in this study of archived telephone contact reports, but needs to be confirmed in additional studies and other patient populations. Until then clinicians should follow accepted clinical practice and maintain a high index of suspicion for considering a diagnosis of NMS.

Keywords: neuroleptic malignant syndrome, diagnosis

203. Environmental Risk Factors for Toxoplasma Gondii Seropositivity in the Old Order Amish

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Background: Toxoplasma gondii (T. gondii) infects all warm-blooded species. T. gondii seropositivity has been previously associated with schizophrenia, bipolar disorder, suicidal behavior, accidents, cognitive deficits, trait impulsivity and aggression. The long-term goal of our project is to define intersections between exogenous and endogenous (pathogen and host) risk factors for T. gondii infection. A high T. gondii seroprevalence (~50%) in the Old Order Amish, collected human genomic data, and the capability of future longitudinal follow up for seroconversion and reactivation offer unique opportunities to identify modifiable risk factors. The current study analyzes risk of seropositivity related to soil, water, food, and animal exposures in the Amish.

Methods: 843 participants in the Amish Wellness Program (336 men and 507 women, mean age = 46.6 ± 16.8) had T. gondii IgG titers measured by ELISA and a risk factor exposure questionnaire obtained. 478 participants (56.7%) were seropositive. Logistic regression was used to test the association between seropositivity and risk factors, adjusting for age and sex.

Results: Seropositive status was associated with cleaning a cat litter box (OR 2.30, 95% CI 1.08-4.57), working with animals (OR 1.61, 1.02-2.56 and OR 2.19, 1.17-4.10 respectively), or consuming unpasteurized milk/yogurt (OR 1.74, 1.14-2.66). After including all individual significant risk factors in model, only eating raw meat (OR 3.10, 1.15-8.34) remained significant.

Conclusions: To be tested in future a large scale interventional longitudinal study, targeted educational efforts to reduce raw meat consumption in a seronegative young individuals may result in lowering seroconversion rates and, perhaps, in the long-run, of T. gondii-linked psychiatric conditions.

Supported By: This work was supported by the Joint Institute for Food Safety and Applied Nutrition, College Park, MD through the cooperative agreement FDU.001418 (PI Postolache).

Keywords: Toxoplasma gondii, Risk factors, Food, Meat, Old Order Amish

204. Living in a Low Socioeconomic Status Neighborhood Increases Risk of Developing Clinically Significant PTSD Symptoms after Motor Vehicle Collision: Results of a Prospective Cohort Study

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Background: Low neighborhood socioeconomic status (nSES) has been associated with adverse effects on stress system function and increased incidence of stress-related disorders following trauma. To our knowledge no prospective studies have evaluated the ability of nSES to predict Post-Traumatic Stress Disorder (PTSD) outcomes after one of the most common forms of trauma, motor vehicle collision (MVC).

Methods: African Americans ≥18 years of age presenting to one of 14 Emergency Departments (ED) in 6 states within 24 hours of MVC who did not require hospital admission were enrolled. ED assessment included collection of participant sociodemographic characteristics and home address. Six-month follow-up assessment included an evaluation of PTSD symptoms (IES-R). IES-R score ≥33 was used to define clinically-significant PTSD symptoms. Participant addresses were geocoded and matched with 2010 U.S. Census Bureau’s SAIPED data. nSES was calculated using SAIPED data and split into quartiles; the bottom two quartiles were collapsed due to small sample size. Log binomial regression analysis was used to assess the influence of nSES on the presence of clinically significant PTSD symptoms six months after MVC, controlling for individual sociodemographic factors (age, sex, education, income, and employment).

Results: 907 participants were enrolled; 786 (87%) completed six month follow up. nSES predicted clinically-significant PTSD symptoms six months after MVC (low v. high nSES, RR (95% CI): 1.38 (1.05, 1.81) high-middle v. high nSES, RR (95% CI): 1.19 (0.87, 1.62)).

Conclusions: After controlling for a range of individual-level factors, low nSES individuals experiencing MVC were at increased risk of developing clinically-significant PTSD symptoms.

Supported By: R01AR060852

Keywords: socioeconomic status, PTSD - Posttraumatic Stress Disorder, motor vehicle collision
205. Strangulation during Sexual Assault Predicts Increased PTSD Symptoms Six Weeks after Assault  

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**Background:** Sexual assault (SA) is common, but to date no large multisite prospective studies of SA survivors have been performed, and little data exists regarding the relationship between assault characteristics and outcomes.  

**Methods:** Women SA survivors ≥18 years of age who presented within 72 hours of assault to one of the 12 US sites in the Better Tomorrow Network were enrolled. Participants completed a short survey at time of the initial SANE exam and follow-up surveys at 1 week, 6 weeks, 6 months and 1 year. Assault-related characteristics were obtained from the medical record. Outcome assessments included PTSD symptom assessment (DSM-IV PCL) at six weeks.  

**Results:** To date in this ongoing study, 299 and 189 SA survivors have completed initial and full study enrollment, 96 SA survivors had medical record data extracted and entered, and 85/96 (89%) have reached/completed six-week follow-up (mean [SD] age = 28 (9.6)). In general, among SA survivors there was little association between PTSD symptom severity at six weeks and the presence or absence of specific assault-related characteristics [drug-facilitated sexual assault (31/85, 37%), known assailant (49/85, 58%), assailant possession of weapon (9/85, 11%)], with point estimate differences in PTSD severity with or without particular assault-related characteristics being much smaller than the 10 point threshold for a clinically significant change in the PCL. Strangulation during assault (16/85, 19%) was associated with significantly higher PTSD symptoms at six weeks [57.8 (17.4) vs. 47.6 (16.8), p < 0.05].  

**Conclusions:** Strangulation-associated SA, but not other SA-related characteristics, predict increased PTSD symptoms six weeks after assault.  

**Supported By:** R01AR060852; R01AR056328  

**Keywords:** PTSD, Sexual Assault, Strangulation  


**Aditi Borde**, 1 Michael Bien, 2 Sean Flannigan, 3 April Soward, 4 Michael Kurz, 5 Phyllis Hendry, 6 Erin Zimny, 7 Christopher Lewandowski, 8 Marc-Anthony Velilla, 9 Kathia Damiron, 10 Claire Pearson, 11 Robert Domeier, 12 Sangeeta Kaushik, 13 James Feldman, 14 Mark Rosenberg, 15 Jeffrey Jones, 16 Robert Swor, 17 Niels Rathlev, 18 David Peak, 19 David Lee, 20 and Samuel McLean  

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**Background:** Motor vehicle collision (MVC) is one of the most common life-threatening events experienced by US civilians. To our knowledge, no prospective studies have compared PTSD outcomes in African Americans (AAs) vs. European Americans (EAs) experiencing MVC.  

**Methods:** Two sister studies enrolled AAs and EAs presenting to one of 16 emergency departments (EDs) in 9 states within 24 hours of MVC who did not require hospital admission; study protocols of the two studies were nearly identical. ED evaluation included the assessment of sociodemographic characteristics; 6-month follow-up assessment included an evaluation of PTSD symptoms (IES-R; score >33 defined clinically significant PTSD symptoms). Binomial logistic regression analysis was used to evaluate potential ethnic differences in clinically significant PTSD symptoms, adjusting for individual sociodemographic factors.  

**Results:** A total of 1855 participants were enrolled (907 (49%) AA, 948 (51%) EA). Six-month follow-up was completed on 786/907 (87%) AA and 834/948 (88%) EA. Six months after the MVC, clinically significant MVC-related PTSD symptoms were much more common in AAs than EAs [295/786 (38%) AA vs. 122/834 (15%) EA]. After adjustment for individual sociodemographic differences (age, sex, education, income, and employment), ethnicity remained a strong predictor of increased PTSD risk (RR = 2.074, 95% CI 1.66 to 2.59).  

**Conclusions:** These findings suggest that African Americans are at an increased risk of developing clinically significant PTSD symptoms after MVC, even after adjusting for a range of sociodemographic characteristics. Further studies are needed to better understand reasons for ethnic differences in PTSD outcomes after MVC.  

**Supported By:** R01AR060852; R01AR056328  

**Keywords:** PTSD – Posttraumatic Stress Disorder, motor vehicle collision, Ethnicity  

207. Problematic Internet Use (PIU) and Its Relationship with Suicidality in Adolescents  

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**Background:** PIU has been associated with depression in adolescents. Suicidality is a serious, potentially life-threatening
symptom of adolescent depression. Thus, understanding the relationship of suicidality with PIU has clinical significance.

Methods: PubMed, PsycINFO, and Web of Science were searched from inception through October, 2016 using the key words Internet addiction, problematic Internet use, pathological Internet use, and heavy/excessive Internet use combined with the terms suicide, suicidal ideation/attempt behavior. For inclusion, studies had to be in English, have at least 100 subjects, and have a mean age of 18 years or less. Effect sizes were calculated from published data.

Results: 11 cross-sectional studies, 1 case control study, and 1 longitudinal study met inclusion criteria and had a total of 284,405 unique subjects. Seven studies were conducted in Asia, 4 in Europe, 1 in Australia, and 1 in the United States. PIU and suicidality were assessed using 7 and 9 different self-report measures respectively across 13 studies. 5 studies assessed suicidal ideation only, 2 studies assessed attempts only, and 6 studies assessed both. 11 cross-sectional studies found a significant association between PIU and suicidality, but the case control study did not. The longitudinal study was not significant in its final analysis possibly due to a high attrition rate at follow-up. Effect sizes were typically small.

Conclusions: Conclusion: Although methodology varied considerably among studies, most of these early studies supported a positive relationship between PIU and suicidality. Further longitudinal study with improved methodology is needed to determine whether PIU is causally related to suicidality.

Keywords: problematic Internet use, Suicidal ideation, suicide attempts, suicidality, adolescents

208. The Contribution of Attention-Deficit/Hyperactivity Disorder Common Genetic Risk Variants to Childhood Irritability: Evidence from Clinical and Population Cohorts

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Background: Severe, childhood irritability is a common feature of neurodevelopmental disorders including Attention-Deficit/Hyperactivity Disorder (ADHD). Twin studies suggest that ADHD and irritability share genetic aetiology. However, other studies have highlighted genetic and longitudinal links between childhood irritability and later depression. This study aimed to test whether common genetic variants associated with ADHD diagnosis, indexed by polygenic risk scores (PRS), were associated with childhood irritability.

Methods: Three UK samples were utilised: two population-based (n=14,701 and ~17,000) and one clinical ADHD sample (n=696). ADHD polygenic risk scores were derived from the largest published ADHD genome-wide association data-set (5,621 cases and 13,589 controls) and generated in each sample. Associations between ADHD PRS and parent rated presence/absence of childhood irritability were examined.

Results: In both population-based samples the prevalence of irritability decreased from childhood (age 7) to adolescence (age 15/16) in males, and increased in females; childhood irritability was more likely to be present in males than females. ADHD PRS were associated with presence of childhood irritability in all three samples (population based samples: OR=1.08, 95% CI=1.01-1.14, p=0.018 and OR=1.13, 95% CI=1.02-1.25, p=0.025, clinical sample: OR=1.38, 95% CI=1.31-1.85, p=0.030). The associations were no longer significant on reaching adolescence in the population based-samples.

Conclusions: ADHD genetic risk may have pleiotropic effects on childhood irritability. Further work is needed to better understand the nature of the relationship between irritability and ADHD, including the possibility that, in childhood, irritability is a neurodevelopmental difficulty.

Supported By: Wellcome Trust, Medical Research Council

Keywords: ADHD, Irritability, Childhood, Polygenic Risk Score

209. Parental Age and Offspring Neurocognitive Performance in the Philadelphia Neurodevelopmental Cohort

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Background: There is now abundant evidence that parental age is associated with neurodevelopmental and behavioral disorders in offspring; however, the mechanism for these associations is unknown. A potential explanation for these associations is impaired cognitive function. The aim of this research is to examine the associations between parental age and neurocognitive performance in offspring in a community-based sample of adolescents.

Methods: 8725 youths (ages 8-21 years, one child per family) from the Philadelphia Neurodevelopmental Cohort completed the University of Pennsylvania Computerized Neurocognitive Battery (CNB) that assessed the accuracy and response time of task performance across four domains (complex cognition, episodic memory, executive function, social cognition). Crude and adjusted regression models with parental age predicting offspring neurocognitive performance for demographic factors (age, sex, race of the participant) and social environment (parental education and a proxy for SES).

Results: Increases in parental, maternal, and paternal ages were associated with greater accuracy and speed of all cognitive domains in unadjusted models, except for the speed of episodic memory. After adjustment for demographic factors and the social environment, the only significant associations were between maternal and parental age and the speed of complex cognition.

Conclusions: To our knowledge, this is the largest study in the US to examine parental age and multiple domains of neurocognition in adolescents. These data extend previous research to a community-based sample of youth, and demonstrate that the association between parental age and neurocognitive function may reflect parental and familial environmental factors rather than biologic and genetic factors associated with increased parental age.
**Supported By:** NIMH MH019112, MH089983  
**Keywords:** Neurocognition, Penn computerized neurocognitive battery, Parental Age, neurodevelopmental disorders

### 210. Is Chronotype an Endophenotype for Bipolar Disorder?

**Lara Baez,** Lihong Cui, and Kathleen Merikangas

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**Background:** Evaluation of clinical samples suggests that chronotype, which represents the extent to which a person’s mental and physical peak occurs during the morning/evening hours, may differ among people with Bipolar Disorder (BPD). The aim of this paper is to examine the association and familial aggregation between chronotype with specific mood disorder subtypes in a community based family study.

**Methods:** 387 probands and a subset of 459 of their first degree relatives with direct clinical evaluations in the NIMH Family Study of Affective Spectrum Disorders reported on chronotype assessed by the Composite Score of Morningness (CSM; high score indicates high morningness). Diagnoses of mood disorder subtypes including Bipolar I (BPI), Bipolar II (BPII), and Major Depressive Disorder (MDD) were based on best estimates of diagnostic interviews and family history report. Mixed effect regression models adjusted for age and sex were employed.

**Results:** Probands with BPI and BPII, but not MDD, had significantly lower CSM scores than those with no disorder (p = 0.0009, p = 0.004). There was a significant association between proband and relative CSM (p = 0.0454). Heritability of CSM was 0.2834 (p = 0.0001). CSM was elevated among relatives of probands with BPI disorder (p = 0.05).

**Conclusions:** Our findings suggesting that evening chronotype is more common among those with BPD confirms growing evidence that BPD is a disturbance of circadian rhythm. The familial links between evening chronotype with BPI further indicate that chronotype may be an endophenotype that warrants further investigation, which may have implications for its etiology and pathogenesis.

**Supported By:** NIMH IRP  
**Keywords:** Bipolar Disorder, Mood disorders, Circadian Rhythms, Endophenotype

### 211. Familial Patterns and Sex Differences in Comorbidity between Atypical Depression and Cardiovascular Disease and Risk Factors

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**Background:** Although there is abundant evidence from clinical and community surveys regarding comorbidity of mood disorders and cardiovascular risk factors (CVRFs) and disorders (DX), the mechanisms underlying this association are complex. The objective of this paper is to investigate the alternative mechanisms for comorbidity using a community based family study of mood spectrum disorders.

**Methods:** The sample consisted of 273 adult probands and 505 relatives who were interviewed and participated in clinical evaluations at the NIH Clinical Center. Psychiatric assessment was based on structured diagnostic interviews and CVRFs/DX were based on self-report and clinical and laboratory examinations.

**Results:** The results of mixed regression models that controlled for age and sex revealed that there were familial associations between atypical depression in probands and relatives (OR = 1.75, 1.2-3.0) and all of the CVRFs. Further, relatives of probands with atypical depression were at increased risk of overweight and physical inactivity (OR = 2.98, 1.0-8.6; OR = 2.32, 0.2-1.0, respectively). Conversely, probands with overweight were at increased risk of atypical depression (OR = 1.92, 1.2-3.2). Although there were sex differences in the base rates of CVRF/DX and atypical depression, there were no sex differences in the familial patterns of comorbidity of these conditions.

**Conclusions:** These results suggest that there may be common familial underlying risk factors that lead to atypical depression, overweight and physical inactivity. Independent transmission of the other CVRF/DX and mood disorder subtypes suggests that comorbidity of these conditions can be attributed to causal mechanisms within individuals. These findings have important implications for both treatment and future etiologic studies.

**Supported By:** NIMH, Swiss National Science Foundation  
**Keywords:** Cardiovascular Disease, Mood disorders, Atypical Depression, Family study, Overweight

### 212. Suicidal Ideation and Behavior in Institutions of Higher Learning: Categorizing Levels of Risk

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**Background:** Suicide is the second leading cause of death for college students, with an annual rate of 7.5 per 100,000. The American Foundation for Suicide Prevention (AFSP) developed the Interactive Screening Program (ISP) to support institutions of higher education in engaging students in mental healthcare.

**Methods:** We used Latent Class Analysis (LCA) to identify subgroups of at-risk students from survey data collected through the ISP. LCA was applied to undergraduate student data and an appropriate latent class model was selected. The model was validated on data collected from graduate students.

**Results:** LCA identified 6 subgroups from the undergraduate sample (N = 5654), which we categorized from low to high acute suicide risk by the proportion of members reporting recent thoughts of suicide. The highest risk group (N = 623, 11%) was mostly women (79%), with 66% having recent
thoughts of suicide, 22.5% reporting a prior suicide attempt, and 97.6% endorsing moderately severe or worse depression. Notably, in a second high risk group (N = 662, 12%), 27% endorsed thoughts of suicide and more than half (57%) reported feeling hopeless, yet only 1.5% noted moderately severe or worse depression. When graduate students (N = 1138) were classified using the model, the proportions falling into each class were similar to undergraduates.

**Conclusions:** We identified at-risk groups in the college student population, each with a distinct prevalence of risk factors, including a group of students who would not necessarily be classified as high risk with depression-based screening, but nevertheless appear high-risk on a number of measures.

**Supported By:** American Foundation for Suicide Prevention, P50 MH090964, R01MH109326

**Keywords:** Suicide, Suicidal ideation, Suicide risk factors, College mental health


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**Background:** Reducing meat consumption in pregnancy may cause inadvertent nutritional deficiencies; here we evaluated adverse substance use among adolescent offspring.

**Methods:** Dietary patterns were derived from pregnant women and their 13 year old offspring in the Avon Longitudinal Study of Parents and Children (ALSPAC). Multivariable logistic regression models including potential confounders evaluated adverse alcohol, cannabis and tobacco use of the children at age 15 years. Potential causality was evaluated using maternal allelic variants impacting biological activity of cobalamin (vitamin B12).

**Results:** Lower maternal meat consumption was associated with greater problematic substance use among 15 year old offspring in dose response patterns. Comparing never to daily consumption after adjustment, risks were greater for all; alcohol, odds ratio OR=1.75, 95% CI = [1.23, 2.56], p < 0.001, cannabis OR=2.04, 95% CI = [1.52, 2.70], p < 0.001 and tobacco use OR=2.70, 95% CI = [1.89, 4.00], p < 0.001. Lower meat consumption disproportionally increased the risks of offspring substance misuse among mothers with optimally functional (homozygous) variants (rs1801198) of the gene TCN2 which encodes the vitamin B12 transport protein transcobalamin indicating a causal role for cobalamin deficits. Risks attributable to cobalamin deficits during pregnancy include adverse adolescent alcohol, cannabis, and tobacco use (14%, 37% and 23% respectively).

**Conclusions:** Lower prenatal meat consumption was associated with increased risks of adolescent substance misuse. TCN2 variants specifically implicated cobalamin deficiency regardless of social confounding. By selectively identifying a causal contribution of vitamin B12 insufficiencies, greater meat consumption need not be advised to reduce risk.

**Supported By:** Intramural Program of the National Institute on Alcohol Abuse and Alcoholism

**Keywords:** Vitamin B12, Substance abuse, Pregnancy, Nutrition, Mendelian Randomization

### 214. Hospital Stay in Individuals with Psychotic Disorders and Bipolar Disorders with and without Kush Use Reported at Hospital Admission

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**Background:** Use of synthetic cannabinoid products (commonly referred to as Kush in the Houston area) has become popular and is leading to an increased number of patients presenting to emergency departments and psychiatric hospitals. The purpose of this study is to evaluate the impact of Kush on hospital length of stay (LOS) in individuals with psychotic disorders and bipolar disorders.

**Methods:** We retrospectively examined medical records of 324 individuals admitted to a psychiatric hospital in Houston, TX due to exacerbations of psychotic disorders and bipolar disorders during January 2014 to July 2015. Data on age, sex, race, length of stay, and the results of urine drug tests administered routinely on the patients at the time of admission were collected. The present study used structural equation modeling to estimate the direct and indirect effects of Kush status on LOS.

**Results:** Kush-positive patients (N = 162) and Kush-negative patients (N = 162) were matched on age, race, and gender. Patients in the present study were diagnosed with either a bipolar spectrum disorder (N = 142) or schizophrenia and other psychotic disorders (N = 182) based on DSM-IV. LOS was significantly different between the two groups (mean LOS for Kush-positive patients = 8.7 ± 5.9 days vs. 11.9 ± 10.3 days for Kush-negative patients; p = 0.001).

**Conclusions:** The results suggest that individuals with psychotic disorders and bipolar disorders who also have comorbid Kush use may require shorter inpatient stay during exacerbation of psychosis. Longitudinal studies controlling for treatment with psychotropic medications are warranted.

**Keywords:** Length of Stay, synthetic cannabinoid, Kush, Bipolar Spectrum Disorders, Psychotic Disorders

### 215. Cannabis and Cocaine Use Are Independent Predictors of Phencyclidine (PCP) Use in District of Columbia Urban Population with Lower Socioeconomic Status

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Howard University Hospital
Background: PCP use is prevalent in Washington DC. There has been fluctuation in PCP use in DC areas over time; from the 1980s to 1990s the use of PCP in DC area decreased. Unfortunately, the trend has been increasing. 10% of arrested adults in DC has active PCP urine toxicology screen. Howard University is a unique institution serving mostly underserved African American population. In the current study, we sought to identify the correlates of PCP use in our patient population.

Methods: We obtained data from QI Project that psychiatry resident conduct continuously at Howard University Hospital. We included patients admitted to the inpatient psychiatric services. Of the 1241 patients, we included 132 patients. We reviewed the charts and laboratory workup including UDS results. Tabaco and synthetic cannabinoid use were self-reported. We used chi-square to analyze the association between PCP use and other variables and used linear regression to correct for confounding factors.

Results: Of 132 patients, 40% are males and 7% of the patients has UDS positive for PCP. Our analysis showed that PCP use was positively associated with cannabis and cocaine use ($P<.02$ and $P<.01$ respectively). Regression model taking in account other substances and gender, the relationship between PCP use remained statistically significant.

Conclusions: Use of PCP has been unfortunately consistently higher in DC compared to the rest of the US. In our previous study, cocaine predicts poor outcome for patients maintained in buprenorphine treatment. These results indicate that treatment strategies addressing substance use in DC should take in account co-occurring substance use pattern.

Keywords: PCP, Epidemiology

216. 20-Year Progression of BMI in a County-Wide Cohort People with Schizophrenia and Bipolar Disorder Identified at Their First Episode of Psychosis

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Background: There is increased prevalence of obesity in (SCZ) and bipolar disorder (BPD), leading to disproportionate risk of adverse health conditions. Prospective, long-term weight gain data, however, are scarce.

Methods: We analyzed data from the Suffolk County Mental Health Project cohort of consecutive first admissions with psychosis followed for 20 years, focusing on people with SCZ and BPD. The time course of weight gain was examined using a 2 (group) x 5 (time) MMRM ANOVA, and BMI scores at the (6 months) and second (2 years) assessments were compared to examine whether early overweight predicted later obesity.

Results: There was a statistically significant effect of time, $F(1,210)=68.06$, $p<.001$, and diagnosis on BMI, $F(1,210)=29.18$, $p<.001$, but not the interaction of time x diagnosis, $F(2,210)=0.88$, $p=.48$. Most participants had normal BMIs at the first two assessments. The proportion of BPDs with normal weight stayed at about 50% through year 10. Early overweight was a predictor of eventual obesity for both groups. At the 10 and 20 year follow-ups, approximately 50% of SCZ sample was obese compared to 30% (year 10) and 40% (year 20) of BPD, with greater prevalence of obesity in SCZ at each assessment (all $p<.02$, except for year 20 ($p=.11$)).

Conclusions: Half of the participants with SCZ and 40% with BPD were obese 20 years after first hospitalization for psychosis, considerably higher than the rate for adults in New York State (27%). Early intervention may be required to prevent long-term consequences of obesity-related morbidity and mortality.

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Keywords: First episode schizophrenia, Bipolar Spectrum Disorders, Weight Gain, Metabolic syndrome, Prospective cohort

217. REM/NREM Sleep-Dependent OSA: What Makes the Difference?

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Background: Obstructive sleep apnea (OSA) was usually known to be worse in REM sleep. However many cases that showed a higher NREM-AHI than REM-AHI were reported. We did not know the meanings of REM/NREM sleep-dependent OSA yet.

Methods: 572 adult OSA subjects confirmed by nocturnal polysomnography were recruited. All patients were classified into 3 groups according to the ratio of 2 or more between REM-AHI and NREM-AHI. 1) REM sleep-dependent OSA (REM-OSA), 2) NREM sleep-dependent OSA (NREM-OSA), 3) sleep stage independent OSA (IND-OSA). Chi-square test, ANOVA, and logistic regression analysis was performed to find meaningful risk factors for each group.

Results: The numbers of REM-OSA were decreased and those of NREM-OSA and IND-OSA were increased with an increase in AHI. Female (OR: 3.543), the percentage of supine position (OR: 1.037) were related to REM-OSA. Age (OR: 1.031), severity of AHI (OR; mild to moderate: 3.860, mild to severe: 2.890) were related to NREM-OSA. And the percentage of snoring time (OR: 1.011), and severity of AHI (OR of mild to severe: 8.389, OR of mild to moderate: 1.914) were related to IND-OSA.

Conclusions: REM-OSA was more frequent in mild OSA. Some features of female gender might be related to REM-OSA. Age as a risk factor for NREM-OSA suggested the possible relation of NREM-OSA with the aging process. Unexpectedly BMI did not increase OR of each groups, though a highest BMI in IND-OSA group.

Keywords: Obstructive sleep apnea, Rapid eye movement sleep, Non-rapid eye movement sleep

218. Posttraumatic Stress Disorder (PTSD) with Nightmares is Associated with a Significantly Lower Frequency of Suicidal Behavior: Results from a Nationally Representative US Sample

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Background: Nightmares (NM) are one of the core symptoms of PTSD (DSM-5). NM have been associated with rapid eye movement (REM) sleep. It is recognized that REM sleep plays a central role in emotional regulation. We examined the frequency of suicidal behavior (SB) and depression in PTSD patients who sought medical attention for nightmares (PTSD+NM) versus all other PTSD visits (PTSD-NM), in a nationally representative US sample.

Methods: We examined an estimated:±SE 27,588,109±2,900,885 (unweighted count=3341) PTSD-related patient visits (mean ± SE age: 39.28±0.65 years; 67.0% ±2.1%, female) from 1995-2011 in the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey. Each patient visit is assigned up to 3 ICD9CM diagnoses and up to 3 ‘Reasons for Visit’ (RFV). Variables were defined as follows: PTSD – ICD9CM code 309.81; Nightmares (NM)- ICD9CM code 307.49 or RFV ‘Nightmares’; Suicidal Behavior (SB)- ICD9CM codes E950-E959 or RFV ‘Suicide attempt’or ‘Intentional overdose’; Depression- ICD9CM codes 296.2, 296.3, 296.82, 311, 296.20-296.36, 300.4.

Results: There were an estimated:±SE 475,169±143,660 (unweighted count=57; 1.8% ± 0.4% of all PTSD visits) NM visits and an estimated:±SE 93,813±40,633 (unweighted count=31; 0.3% ± 0.1% of all PTSD visits) SB visits. Interestingly, there was no SB in the PTSD+NM group. Depression was not significantly different between the PTSD+NM versus PTSD-NM groups (OR=1.43, 95% CI 0.77-2.65).

Conclusions: PTSD patients with NM had significantly less SB but not lower depression scores. This previously unreported finding suggests that NM (possibly through mechanisms associated with REM sleep) have a protective effect against SB.

Keywords: PTSD, Nightmares, Emotional Regulation, REM sleep, Suicide

219. HAB/LAB Rats – A Model of Opioid Tone
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Background: Rats bred for anxiety based on their performance on an elevated plus maze have been considered the gold standard genetic animal model for anxiety. However, many of the behaviors observed in these rats – including alcohol self-administration, pain tolerance, and aggression – are the opposite of what we have observed in humans with chronic anxiety. Interestingly, monogamous voles (MV) and polygamous voles (PV) mirror the behavioral profiles of HAB and LAB rats.

Methods: Literature on both animal models was reviewed by search on PUBMED. The terms “HAB rats”, “polygamous voles”, “AVP and opioid” articles were reviewed on PUBMED as both animal models have AVP mutations and display behaviors that are known to be controlled by the endogenous opioid system.

Results: These two animal models have different AVP mutations which lead to the same physiological outcome. HAB/PVs have higher levels of AVP activity, while comparatively LAB/MVs have lower levels of AVP activity. This leads to different baseline levels of endorphins affecting a range of behaviors such as bonding, addiction, pain sensitivity and aggression.

Conclusions: While HAB rats exhibit traits of chronic anxiety, it is not the result of an “anxiety gene” it is simply an example of stress-diathesis. The genetic make-up of the HAB group gives them higher opioid tone (via greater AVP activity) making the lab environment, one of forced social interaction, an adverse environment with no way for the rats to naturally modulate their endogenous opioid levels to lower, less dysphoric levels and inducing chronic anxiety.

Keywords: anxiety, attachment, opioid, addiction, AVP

220. Molecular Indicators of Stress-Induced Neuroinflammation in a Mouse Model Simulating Features of Post-Traumatic Stress Disorder
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Background: PTSD is a growing problem. Identification of targets for early intervention requires understanding of pathogenesis. Accordingly, we examined alterations in signaling pathways following exposure to stress.

Methods: A social-stress model involving exposure of an intruder (male C57BL/6) mouse to a resident aggressor (male SJL) mouse was used to simulate features of PTSD. Transcriptome changes in the blood, brain regions and spleen, as well as DNA methylome changes in hemi-brain of stressed vs control C57BL/6 mice were assayed at one, 10 and 42 days post-trauma. Transcripts and methylation states meeting criteria p < 0.01 and fold changes > 2 were used to identify enriched pathways and processes.

Results: Differentially expressed genes (DEGs) and methylated promoter regions were associated with activated inflammatory pathways (IP), inhibited neurogenesis (NG) and synaptic plasticity (SP). In amygdala (AY), hippocampus (HC), and medial prefrontal cortex (MPFC), all 3 pathways were activated during the early response. While NG/SP were inhibited at later times in AY, they persisted at 42 days post-trauma. Transcripts and methylation states meeting criteria p < 0.01 and fold changes > 2 were used to identify enriched pathways and processes.

Supported By: MOMRP/TAWT/869
Keywords: PTSD MICE GENES BRAIN BLOOD

221. Interaction of Early Life Stress (ELS) + Short Allele of Serotonin Transporter Gene (STG) and Reduced Macaque Neurogenesis
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Keywords: anxiety, attachment, opioid, addiction, AVP
Background: Lifetime adversity coupled with the short allele of the STG [G X E (gene x environment) interaction] is associated with depression. ELS adversely impacts neuroplasticity including hippocampal neurogenesis. We examined the effect of STG polymorphisms on neurogenesis following ELS.

Methods: 25 adult male macaques [mean (SD) weight = 9.86 (2.67) kg; mean (SD) age = 8.48 (1.45) years] were included. Nine were reared under randomly-assigned variable foraging demand (VFD) conditions, a form of ELS. Six of 9 VFD had the heterozygote short allele whereas 0 of 16 of non-VFD had the short allele (p = 0.005). Doublecortin counts were quantified and logarithmically converted.

Results: Adult male macaques with one short allele + ELS exposure were found to have significantly reduced neurogenesis [N=6, log doublecortin mean (SE) = 2.54 (0.49)] versus remainder [N=19, mean (SE) = 4.63 (0.28); F(1, 23) = 6.87, p = .015]. Results were confirmed parametrically [z-score = 2.16; p = 0.03]. There were no weight or age differences. (p>.15).

Conclusions: ELS + short allele of STG was associated with reduced neurogenesis in adult male macaques in a grouping where there were no age and weight differences. However, the lack of short allele + non-VFD subjects prohibited assessment of G X E interactions. Our data are consistent with diverse biobehavioral G X E interactive effects for behavioral timidity to intruder (↑), CSF CRF (↑), amygdala volume (↑) and corpus callosum cross-sectional area (↑). Our data are consistent with human GxE interactions indicating depression following life adversity in vulnerable polymorphisms.

Supported By: RO1 MH

Keywords: Early Life Stress, Serotonin Transporter Gene, Neurogenesis, Depression, Macaques

222. Functional Studies of the Ankryin3 Bipolar Disorder GWAS Gene in Mouse and Neuronal Models

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Background: Genome-wide association studies have implicated the ankryin3 gene (ANK3) in susceptibility to bipolar disorder (BD). Ankryin3 encodes the ankryinG protein that tethers membrane proteins to the cytoskeleton, which is critical for many neuronal functions such as action potential firing, intracellular transport, and synaptic transmission. However, the mechanism of ankryin3 in BD is unknown.

Methods: We are using neuronal and mouse models to investigate ankryin3 function in the brain. Using conventional transgenic and RNA interference methods, we are examining the behavioral, neurobiological, and physiological effects of modulating ankryin3 expression in mouse brain. CRISPR/dCas9 technology is being used to modulate transcription of ankryin3 in a neuronal cell line to examine molecular mechanisms.

Results: Ankryin3 reduction in mouse brain induces a range of behavioral changes, including increased impulsivity, motivation, and stress sensitivity. Ank3+/-- heterozygous knockout mice have 50% fewer cfos-positive neurons while exhibiting impulsive behavior (p < 0.01), indicating lower hippocampal neuronal activity, compared to wild-type Ank3+/+ mice. Both the behavioral and neuronal activity changes in Ank3+/-- mice are normalized by lithium treatment, supporting the disease relevance of these findings. Molecular analyses implicate kinesin-mediated transport and glutamate signaling as mediators of the behavioral and neuronal abnormalities in Ank3+/-- mice.

Conclusions: Behavioral and neurobiological alterations induced by ankryin3 repression support the involvement of this gene in BD, and provide new insight into its role in regulating brain function. These studies support the investigation of genetic risk factors using mouse and neuronal models to elucidate the neurobiological mechanisms underlying BD.

Supported By: R21MH100570; Stanley Medical Research Institute; NARSAD; European Commission

Keywords: Mouse model, Animal Behavior, Hippocampus, CRISPR, Lithium

223. Genome-Wide Association Study of Posttraumatic Stress Disorder Symptom Domains in Two Cohorts of United States Army Soldiers

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Background: Posttraumatic stress disorder (PTSD) is a serious public health concern. Genome-wide association study (GWAS) of PTSD can provide insight into its etiology. Several GWAS on PTSD diagnosis have been published, including our GWAS on PTSD in the Army Study of Risk and Resilience in Servicemembers (Army STARRS). PTSD is a complex syndrome comprising several symptom domains. To better understand the etiology of PTSD, we performed genome-wide analysis for PTSD symptom domains in Army STARRS.

Methods: We performed genome-wide analysis in 8,920 European American, 1,932 African American, and 2,622 Latino American samples with traumatic experiences. The lifetime severity of three PTSD symptom domains (re-experiencing, avoidance, and hyperarousal) were collected using the PTSD Checklist (abbreviated version). The association analyses were performed using linear regression
adjusted for 10 principal components of ancestry, age, and gender. SNP-based heritability and genetic correlation among domains was estimated in the European American subsample.

**Results:** None of the genome-wide analyses showed evidence of confounding by ancestry (lambda_GC from 0.99 to 1.02). We identified 1 locus for re-experiencing severity in the European American sample (chr. 18, rs2311207, Beta=0.2260, P=2.5x10^-8). SNP-based heritability were 0.060 for re-experiencing (P=0.070), 0.043 for avoidance (P=0.138) and 0.085 for hyperarousal (P=0.019) symptoms. We observed strong genetic correlations between the three PTSD symptom domains (0.80 to 1.00).

**Conclusions:** We identified 1 locus for PTSD re-experiencing severity in European American. Our analyses suggest modest SNP-based heritability but strong genetic correlations among PTSD symptom domains, suggesting predominantly shared contributions of common variation. Replications of these results in independent samples are warranted.

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**Keywords:** PTSD Symptom Severity, Military soldiers, GWAS, SNP-based heritability, Genetic correlation

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**224. Examining Mitochondrial Genetic Dysfunction in Obsessive Compulsive Disorder**

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**Background:** Obsessive-compulsive disorder (OCD) is a severe neuropsychiatric disorder that has strong genetic risk, but the precise factors remain to be identified. Mitochondria play crucial roles in neurons, such as Ca2+ regulation, redox signaling, and apoptosis. The importance of mitochondria in neurons is evident from the reported comorbidity between mitochondrial diseases and neuropsychiatric symptomatology. Here we examined the role of nuclear-encoded oxidative phosphorylation related genes in OCD risk and its sub-phenotypes.

**Methods:** We selected 28 genes involved in oxidative phosphorylation or in oxidative stress, mitochondrial biogenesis, inflammation and apoptosis. A total of 59 SNPs were analyzed in 477 OCD subjects and 379 healthy controls. Logistic regression was used for OCD risk analysis and linear regression was used to test association with the sub-phenotypes of interest: age at onset (AAO) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) 6-factor symptom dimensional factors derived from the Y-BOCS symptom checklist using principal components analysis.

**Results:** From case-control analysis, we observed nominally significant association for the SNPs rs4011457 in the NDUFS7 gene and OCD risk (N=856, P(uncorrected)= 0.004). Also, nominally significant evidence for association was observed for the SNP rs3820189 in the 5’of the MFN2 gene and YBOCS total score (N=346; P(uncorrected)= 0.002) and for the SNP rs4246944 in the PPIF gene and Sex/Religion factor (N=371; P(uncorrected)= 0.002). A permutation-based test of all 59 SNPs jointly showed significant association with OCD (P(perm)=0.003).

**Conclusions:** To the best of our knowledge, this is the first study to show evidence that nuclear-encoded mitochondrial genes may influence OCD.

**Keywords:** Mitochondria, Neurogenetics, Obsessive Compulsive Disorder (OCD), Genetic Association, Mitochondrial dysfunction

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**225. Psychosocial and Genetic Correlates of Psychological Resilience in World Trade Center Rescue and Recovery Workers**

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**Background:** While many WTC responders developed trauma-related psychiatric disorders, a majority demonstrated psychological resilience or recovery despite enduring severe trauma. This study evaluated potentially protective factors associated with resilience in WTC responders.

**Methods:** Participants (n=307) recruited from a diverse cohort of WTC responders monitored at the WTC Health Program completed a clinician-administered interview (CAPS-DSM-IV), self-report scales (BDI-II, STAI-Trait, MOS Social Support Survey, Life Orientation Test-Revised, Coping Self-Efficacy Scale), and blood sample collection. Predominant responder groups were identified using cluster analysis based on number of ten WTC-related exposures (e.g., exposure to human remains) and current stress-related psychopathology (composite of WTC-related PTSD, depressive and anxiety symptoms). Two FKBP5 SNPs (rs1360780, rs9296158) were genotyped in 193 responders.

**Results:** A three-group solution best fit the data (BIC=276.65, BIC change = −56.91): Control (low WTC exposure number–low symptoms; 49.9%); Resilient (high exposure number–low symptoms; 22.1%). Compared to Distressed responders, Resilient responders scored significantly higher on coping self-efficacy (d=1.64), dispositional optimism (d=1.50), and social support (affectionate support; d=1.18). Compared to Control responders, Resilient responders were younger but did not differ on psychosocial measures. In the subsample with FKBP5 genotype data, number of major–protective alleles was significantly associated with Resilient vs. Distressed group membership (ORs=1.83-1.87).

**Conclusions:** Interventions to enhance coping self-efficacy, social support, and positive outlook might help promote resilience and recovery in WTC and other disaster responders. Further, FKBP5 genotype might moderate the association between trauma exposure and resilience in this population.

**Supported By:** NIOSH

**Keywords:** PTSD - Posttraumatic Stress Disorder, FKBP5, Psychosocial Stress, Genetics, World Trade Center responders
226. Whole Exome Sequencing (WES) in a Case-control Post Traumatic Stress Disorder (PTSD) Cohort

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**Background:** PTSD is highly prevalent in a traumatized community of inner-city Atlanta (Grady Trauma Project, GTP). Genetic heritability accounts for 30-40% of the PTSD risk and rare genetic variants of large effect could be associated to its etiology.

**Methods:** 30 similar trauma-exposed females with opposite phenotypes were selected for WES from the GTP. They have similar age, education, employment status, and depression treatment. The samples were selected for complete deep-behavioral phenotypes, in addition to other biological biomarkers (e.g. cortisol-measures) and mRNA-microarray. WES was performed at BHCMG. Variant analysis was performed using the PhenoDB. 14 cases and 15 controls were successfully sequenced.

**Results:** We performed an autosomal dominant and recessive (homozygous and compound-heterozygous) analysis for each sample. Genes mutated in 3 or more cases were selected and the respective genes prioritized based on information available in ClinVar, HGMD, OMIM, MGI, and GWAS catalog. In controls, the average-number of single nucleotide variants (SNVs) was 165557: 1805 were frameshift deletion/insertion 1962 nonframeshift deletions/insertions, 49120 nonsynonyms SNVs, 47386 synonymous SNVs, 700 stop-gains, 95 stop-loss. In cases, SNVs average was 190123: 1823 frameshift deletion/insertion 1991 nonframeshift deletions/insertions, 50596 non synonymous SNVs, 48794 synonymous SNVs, 693 stop-gain SNVs, 100 stop-loss SNVs. Next, we will a) compare genes identified among cases to controls b) select the mutated genes that are unique to the cases for further functional studies.

**Conclusions:** To our knowledge, this is one of the first studies to attempt to identify rare variants associated with PTSD. We anticipate further analysis will uncover new variants Genes involved in the biology of PTSD.

**Supported By:** NIH R01MH094757, R01MH096764, NHGRI 1U54HG006542.

**Keywords:** PTSD - Posttraumatic Stress Disorder, exome sequencing, Rare variants

227. Validation Study in Two Genome-Wide Significant Risk Variants for Antipsychotic-Induced Weight Gain

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**Background:** Antipsychotic-induced weight gain (AIWG) is a leading factor of patient non-compliance and metabolic dysfunction. Numerous twin and candidate gene studies suggest a role of genetic factors in overall risk of AIWG development. Genome-wide association studies (GWAS) are a hypothesis-free approach that allow us to find novel variants associated with the phenotype of interest. A recent GWAS performed on a Han Chinese sample suggested a possible role of rs1097714 and rs10977154 variants of the protein tyrosine phosphatase, receptor type D (PTPRD) gene and AIWG. Aim: The current study intends to replicate results from the recent GWAS indicating a role of variants PTPRD and TCP11 genes in Han-Chinese population.

**Methods:** We investigated associations between top variants from a recent GWAS and percentage of weight/BMI change in two independent samples of European ancestry using ANCOVA. Sample 1 included 151 with schizophrenia or schizoaffective disorder (64.2% male), 34 of which demonstrated AIWG (weight increase more than 7% from baseline to the final time point). Sample 2 included 189 patients (79.9% male) 31 of which demonstrated AIWG.

**Results:** None of twenty top variants showed any effect in our first sample. In the second sample, we found nominal effects of two TCP11 variants rs1886243 (p=0.037) and rs6915627 (p=0.033) on percentage of BMI change. Nevertheless, none of our results remained significant when corrected for multiple testing.

**Conclusions:** Our results tentatively suggest that variants in TCP11 but not PTPRD modulate AIWG in European population.

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Background: Evidence suggests that there is a distinct neuro-cluster (biotype) of psychosis. Individuals in the ‘globally impaired’ neuro-cluster exhibited deficits on a constellation of event-related potential (ERP) measures. In this study, we investigated the genetic underpinning of globally impaired neuro-cluster. We constructed genome-wide polygenic scores (GPS) to examine the shared genetic components between globally impaired ERP and other related phenotypes, and established the potential causal mechanisms between genes, the ERP, and clinical features.

Methods: We empirically derived the ‘globally impaired’ (n=60) and the ‘other’ clusters (n=323) from a sample of schizophrenic (SCZ=136), bipolar (BPD=121) patients, and healthy individuals (n=126) according to six ERP phenotypes, using the K-means algorithm. We used published GWAS results of SCZ, BPD, college completion, and childhood intelligence as the discovery datasets to derive GPS for each phenotype in our study sample and tested associations between each GPS and being in the “globally impaired” cluster. We conducted causal mediation analyses to estimate the proportion of polygenic effect on clinical features mediated through globally impaired membership.

Results: Globally impaired ERP was associated with higher PANSS-positive score (P=0.005). We found a significant positive association between the college-GPS (PT=0.01) and globally impaired ERP (FDR-corrected P=0.004; R2=6.15%). The SCZ-GPS (PT=0.001) was also associated with globally impaired ERP (unadjusted P=0.010; R2=3.07%). The effect of college-GPS on PANSS-positive was almost entirely mediated through globally impaired ERP (proportion=97.1%).

Conclusions: Results demonstrated polygenic pleiotropy and causal relationships between higher educational attainment, globally impaired ERP, and positive symptoms. The globally impaired ERP might be a useful endophenotype for positive symptoms.

Supported By: NIMH R01
Keywords: genome-wide polygenic scores, event-related potential, Pleiotropy, schizophrenia, bipolar disorder

229. Genome-Wide Association and Polygenic Genetic Correlation Analyses of Real-Life Community Functioning in Patients with Psychotic Disorders

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Background: Community functioning plays a key role in determining prognosis and quality of life. Genetic studies of functional impairment in psychiatric disorders are scarce. In this study, we collected community functioning using the Multnomah Community Ability Scale in patients with psychotic spectrum disorders and controls. Our goals were to: i) estimate the SNP-based heritability of two domains of real-life functioning: independent living/meaningful activity and social competence and ii) examine the shared genetic components between real-life functioning and other related phenotypes.

Methods: After quality control and genotype imputation, 508 participants were included in the analyses (494 patients and 14 controls). We carried out SNP-based heritability analyses for each domain of functioning. We estimated genetic correlation between the measure for the independence of living domain, subjective well-being, and cognitive function, as well as schizophrenia, bipolar, and MDD risk, using LD score regression.

Results: SNP-based heritability was estimated to be 1 (p=0.26) for independent living and 0 (p=1) for social competence, respectively. Genetic correlations of independent living with subjective well-being was estimated to be 0.31 (p=0.23), with cognitive function, -0.31 (p=0.23), with schizophrenia, -0.27 (p=0.13), with bipolar disorder, -0.28 (p=0.24), and with MDD, -0.61 (p=0.15).

Conclusions: Results suggest that independent living has higher SNP-based heritability than the social competence functioning, although the findings are only trends. Higher risk of schizophrenia, bipolar and MDD is genetically correlated with lower independent functioning, whereas lower cognition and better subjective wellbeing are genetically correlated with higher independent functioning. We observed the greatest shared genetic components between independent living functioning and MDD.

Supported By: R01MH1109687
Keywords: SNP-based heritability, Polygenic genetic correlation, Community functioning, Psychotic disorder

230. Transcriptome-wide Analysis Identified Differential Expression of P1D1, a Gene Implicated in Insulin Resistance, in High versus Low Psychological Resilience

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Background: We investigated differential gene expression profiles between individuals with high and low self-report resilience.
Methods: Resilience was assessed with the 10-item Connor-Davidson Resilience Scale (CD-RISC). High resilience was defined as having the CDRISC score in the upper third, and low resilience as having CDRISC score in the lower third of the overall Grady Trauma Project sample. We included only African American (AA) participants to reduce ethnic heterogeneity. Gene expression was generated on Illumina HumanHT-12 BeadChip arrays. Transcriptome-wide differential analysis was performed for high vs. low resilience groups, adjusting for sex, age, current drug and alcohol use, history of childhood maltreatment, and genotypic principal components.

Results: A total of 237 AA participants were available for the analysis (124 low and 113 high resilience; 51 male and 186 female). At transcriptome-wide FDR < 0.05, one gene, phosphotyrosine interaction domain containing 1 (PID1), had significantly higher expression in low resilience group compared to high resilience group after adjusting simultaneously for sex, age, current drug and alcohol use, history of childhood maltreatment, and population stratification.

Conclusions: Over-expression of PID1 (seen in low resilience group here) has been shown to lead to insulin resistance. Insulin resistance is a feature of metabolic syndrome and important risk factor for cardiovascular diseases and diabetes. Our findings suggest that self-perception of one’s resiliency is associated with objective marker of cardiovascular disease and diabetes risks, underscoring an important connection between positive sense of self and physical health outcomes, and potentially identifying a psychological target for behavioral intervention.

Supported By: MH096764; MH071537; IK2CX000601

Keywords: Resilience, genome-wide gene expression, insulin resistance

231. Serotonin Transporter Gene Methylation and Antidepressant Treatment of Major Depressive Disorder

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Background: The current process used to prescribe antidepressant medication is markedly inefficient, as more than 50% of treated patients fail to reach remission. Antidepressant treatment success has been associated with genetic variation, but studies are not well replicated and epigenetic mechanisms remain under investigated at this time. DNA methylation, an epigenetic modification, may provide more information regarding antidepressant response and guide physicians in choosing the most effective medication for each patient. We investigated the influence of the 5-HTT methylation on antidepressant response in our sample.

Methods: Caucasian depression patients (n=213) were selected from a large discovery sample (IMPACT, N=7,000). DNA modification profiles were interrogated using the Infinium HumanMethylation450 Beadchip array. Nine CpG probes located near the 5-HTT promoter were used to quantify methylation levels. Additionally, patients were genotyped for the functional 5-HTTLPR variant. Change in Beck Depression Inventory (BDI) score was used to measure antidepressant response and remission over eight weeks. The relationship between methylation levels and antidepressant response was modeled using linear regression analyses.

Results: Decreased methylation of the 5-HTT gene was nominally associated with response to antidepressants in our sample. The effect was driven by cg05016953, located in exon 1A, which was associated with greater improvement in BDI score over eight weeks (F(3,209)=3.38, p=0.02), 5-HTTLPR genotype was neither associated with 5-HTT DNA methylation nor antidepressant treatment response.

Conclusions: 5-HTT DNA methylation may be associated with therapeutic response to antidepressant medication. Typically, hypomethylation in the promoter region is associated with increased 5-HTT gene expression, theoretically decreasing 5-HTT availability and positively impacting antidepressant response.

Supported By: Ontario Ministry of Research and Innovation (Dr. Kennedy PI); Genome Canada GAPP (Dr. Kennedy Co-PI).

Keywords: Antidepressant response, Serotonin Transporter Gene, DNA methylation, Pharmacogenetics, Major Depressive Disorder (MDD)

232. Genome-Wide Association Study of Venlafaxine Treatment Remission in Late-Life Depression

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Background: In geriatric depression, antidepressant treatment response is often slow and incomplete; new biomarkers for antidepressant response could lead to precision medicine and uncover new mechanisms of illness. Therefore, we conducted a genome-wide association study (GWAS) in older adults treated with venlafaxine.

Methods: Three-hundred and fifty participants (≥60 years) of mixed ethnic ancestry, diagnosed with major depression (MADRS≥15), were treated with venlafaxine (~12 weeks). Individuals were genotyped using the Illumina PsychArray, and genetic data was imputed to >5 million variants per individual. Associations with remission status (MADRS<10) and change in MADRS score were conducted using logistic/linear regressions, adjusted for ancestry, sex, recruitment site, length in treatment, depressive episode duration, and baseline depressive severity. We also conducted pathway enrichment analysis using DEPICT.
Results: No genome-wide associations were significant at $5 \times 10^{-8}$. Our top hit variant, in a schizophrenia susceptibility gene, showed an association with MADRS score change. This gene has been implicated in 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 genetic variant upstream of neuro-specific gene expressed in the hypothalamus and amygdala, suggesting a role in synaptic neurotransmitter signalling. Our top hit pathways included processes in the metabolic pathway of amyloid precursor protein.

Conclusions: Our findings suggest novel gene variant associations with measures of venlafaxine remission in older adults, as well as, interesting neuro-relevant genetic pathways. A new, larger study of geriatric depression treatment will confirm these novel findings.

Keywords: GWAS, Depression, Venlafaxine, Antidepressant, Genetics

233. BDNF Methylation and Stress Response in a Clinical Population with Major Depressive Disorder

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Background: Major Depressive Disorder (MDD) is a multifactorial disease with a heritability of 35-40%. BDNF Gene Val66Met (rs6265) variant has a well-established role in neuronal plasticity and decreased levels have been observed in MDD. Previous studies support that vulnerability to environmental stress is mediated by the rs6265 variant. Methylation patterns in exon VI of BDNF are emerging as a possible explanation for how Early Life Stress (ELS) can disrupt BDNF expression. However, there is still controversy because most of these studies are in non-clinical populations.

Methods: We present a case-control study in clinical population, with matched controls. Informed consent was provided by all individuals. ELS was assessed by clinical questionnaire and stressful live events questionnaire. The top hit pathways included processes in the metabolic pathway of amyloid precursor protein.

Results: No significant differences were observed in overall methylation patterns between cases and controls. However, methylation in CpG islands 2, 6, 9, 14, 15 and 16 was higher in cases with MDD compared to controls ($P=0.001$). There was association in methylation patterns among controls that experienced ELS ($P=0.005$), however this association was not observed in cases.

Conclusions: Exon IV methylation in specific CpG islands is higher in MDD. Increased methylation in controls with ELS may suggest a predisposition to MDD. Higher methylation in cases may not necessarily be related to ELS. Further sample should be completed to support conclusions.

Supported By: CoLociencias, Los Andes University, ICSN-Clinica Montserrat

Keywords: Major Depression, brain-derived neurotrophic factor, Epigenetics, Early Life Stress

234. Search for Risk Variants in TrkB and BDNF that Predispose to Lithium Responsiveness in Bipolar Disorder

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Background: BDNF and its receptor TrkB have been implicated in bipolar disorder and lithium response. Lithium induces release of BDNF which is essential for its function. We have previously shown that variants in the TrkB gene are associated with lithium response and bipolar disorder. The goal of this study was to identify sequence variants in these two genes that affect the action of lithium in bipolar disorder.

Methods: 73 lithium responsive (LiR) and 47 non-responsive (NR) retrospective samples were used for targeted sequencing of exons and regulatory regions. Samples were combined into pools of 23 to 37 individuals. Paired-end sequencing was done using Custom Amplicons (Illumina). Variants were called with Genome Analysis Toolkit. PLINK was used to calculate a chi-square statistic. Annotation was done using SIFT and PolyPhen-2.

Results: For BDNF, 35 variants were called. Using a conservative Bonferroni correction for 174 comparisons, a statistically significant $p$-value would be $<2.8 \times 10^{-4}$. Two suggestive variants were found for BDNF. For TrkB, 159 variants were called. A minor allele variant was found more frequently than expected in the LiR samples in the promoter region of TrkB, having a $p$-value of 2.93 x 10-6. RegulomeDB predicts this variant is important for transcription factor binding.

Conclusions: Targeted sequencing revealed the over abundance of a minor allele in the promoter of TrkB for LiR but not in NR. Lithium efficacy for the treatment of bipolar disorder is likely to involve the BDNF/TrkB pathway. This study provides a likely candidate region to further investigate the function of lithium in bipolar individuals.

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Keywords: Bipolar Disorder, lithium response, BDNF, NTRK2, Next Generation Sequencing

235. Deep Brain Stimulation Modulates Frontostriatal Inhibitory Control in Obsessive-Compulsive Disorder

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11, Matthijs Vink2, Judy Luigjes1, Guido van Wingen1, and Damiaan Denys1

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely used treatment for severe and treatment-resistant Obsessive-Compulsive Disorder (OCD). DBS for OCD was recently reported to improve performance of executive functioning, specifically working memory and inhibitory control.

Methods: In a randomized, double-blind, sham-controlled study, 10 patients with OCD and a bilateral STN-DBS were assessed before and 6 months after surgery using a computerized dual-tasking behaviour task (Break Inhibition Test – BIT).

Results: Five patients were available for analysis. Significant improvements were observed in performance on the BIT after DBS. This improvement was associated with reductions in OCD symptoms.

Conclusions: DBS for OCD improves inhibitory control in the frontal-striatal circuit, which is consistent with the mechanism of action of DBS for OCD.

Supported By: R25 MH101072

Keywords: Obsessive-Compulsive Disorder, deep brain stimulation, inhibitory control, prefrontal cortex, striatum

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Conclusions: Patients with obsessive-compulsive disorder (OCD) are unable to stop unwanted compulsive behaviors, which has been linked to dysfunctional brain networks of inhibitory control. Deep brain stimulation (DBS) targeted at the ventral limb of the anterior capsule (vALIC) is efficacious for therapy-refractory OCD. Here, we explored if DBS restores sensorimotor frontostriatal pathways that are involved in inhibitory control.

Methods: DBS implanted OCD patients performed a stop-signal with DBS ON and then one week later with DBS OFF. The task included reactive inhibition, i.e. outright stopping in response to a stop-signal, and proactive inhibition, i.e. anticipation of a potential stop signal. We assessed BOLD fMRI activation differences over the two scans between patients (DBS ON and OFF) and 13 matched healthy controls in the right striatum and right inferior frontal cortex.

Results: DBS OFF increased obsessive-compulsive symptoms with 37% (t = -4.36, p = 0.003). Reactive inhibition and frontostriatal activation did not differ between patients (DBS ON or OFF) and controls. Behaviorally, DBS did not significantly change proactive inhibition compared to controls. However, DBS induced significant changes in proactive inhibitory activation in the right striatum (group x scan interaction F1,19 = 5.74, p = 0.027) and right inferior frontal cortex (group x scan interaction F1,19 = 7.63, p = 0.012). Patients with DBS OFF had lower activity in these regions than healthy controls, whereas activity during DBS ON did no longer differ significantly from controls.

Conclusions: DBS normalized frontostriatal activity during proactive inhibition. These results suggest that DBS for OCD interrupts a pathological frontostriatal loop, allowing successful inhibition of unwanted behaviors and restoration of goal-directed actions.

Keywords: Deep Brain Stimulation, Response inhibition, Obsessive Compulsive Disorder (OCD), BOLD fMRI

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236. Inflammation in the Neurocircuitry of Obsessive Compulsive Disorder

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Background: An autoimmune model was proposed for a small minority of obsessive compulsive disorder (OCD) cases associated with Streptococcal infections, however, elevated neuroinflammation could be broadly important in OCD. Identification of a neuroinflammatory phenotype in the brain is possible with positron emission tomography (PET) for measuring translocator protein total distribution volume (TSPO VT), an index of TSPO density. When microglia are activated, TSPO levels are increased. The primary aim of the present study is to apply [18F]FEPPA PET to determine whether TSPO VT is greater in OCD within the dorsal caudate, orbitofrontal cortex (OFC), thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex (ACC).

Methods: [18F]FEPPA PET was applied to measure TSPO VT in the hypothesized regions in OCD participants (n=20) and health (n=20) (matched for age). All participants were antidepressant-free, and had no additional current psychiatric or medical illnesses.

Results: TSPO VT was elevated in OCD within the hypothesized regions by 26.0% - 34.7%. Calculation of analysis of variance resulted in the effects of diagnosis by region: dorsal caudate F1,32 = 14.4, P = .001; OFC F1,32 = 11.3, P = .002; thalamus F1,32 = 13.7, P = .001; ventral striatum F1,32 = 14.7, P < .001; dorsal putamen F1,32 = 13.4, P = .001; and ACC F1,32 = 10.7, P = .002. The Yale-Brown obsessive compulsive scale distress associated with compulsive behaviours subscale score was positively correlated with TSPO VT in the OFC (r = 0.32, P = .005).

Conclusions: This is the first study to demonstrate neuroinflammation in OCD. The most likely interpretation of elevated TSPO levels is microglia activation and an important clinical implication is that this abnormality may be targeted by neuromodulatory therapeutics.

Supported By: CIHR

Keywords: Obsessive Compulsive Disorder (OCD), Positron Emission Tomography, Translocator Protein (TSPO), Neuroinflammation, [18F]FEPPA

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237. PTSD Exposure-Based Treatment Changes Amygdala and Hippocampus Resting State Functional Connectivity in PTSD

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Background: Recent research suggests that posttraumatic stress disorder (PTSD) is associated with decreased amygdala and hippocampal resting-state functional connectivity (rsFC) with the prefrontal cortex (PFC). It remains unknown whether Prolonged Exposure (PE), a first-line, exposure based treatment, can change these connections. We assessed rsFC in patients with PTSD and trauma-exposed healthy controls (TEHCs), investigating the association of a 10-week PE treatment with enhanced rsFC between amygdala and PFC, and between hippocampus and PFC.

Methods: Fifty participants (PTSD=24; TEHC=26) underwent resting functional magnetic resonance imaging (fMRI) scan at baseline and 10 weeks later, during which time patients with PTSD completed PE treatment. RsFC patterns of the amygdala and hippocampus were investigated before and after treatment.
Seed regions of interest (ROIs) included centromedial amygdala (CMA), basolateral amygdala (BLA), and hippocampus.

**Results:** Results: Post- versus pre-treatment comparisons in PTSD patients revealed increased rsFC of the BLA with orbitofrontal cortex (OFC), BLA with medial prefrontal cortex (mPFC), centromedial amygdala (CMA) with OFC, and hippocampus with mPFC. Increased CMA-OFC connectivity was associated with reduced PTSD re-experiencing and avoidance symptoms.

**Conclusions:** Conclusions: PE-induced increases in connectivity and correlations with treatment effects on symptom reduction suggest a neuroanatomical basis for its clinical efficacy. Enhanced amygdala and hippocampus functional connectivity with PFC could underlie improved capacity for inhibition or re-valuation of threat, and heightened memory encoding and retrieval ability, respectively. These findings support further investigation of this circuitry as a therapeutic target in PTSD.

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**Keywords:** Resting state functional connectivity, Resting state fMRI, prolonged exposure, PTSD, Amygdala

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238. Functional Connectivity between BNST and Amygdala is Associated with Irritability/Aggression in PTSD

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**Background:** The bed nucleus of the stria terminalis (BNST) is a portion of the extended amygdala that has been implicated in sustained threat. Recently, methods have been developed to delineate the BNST on MRI scans at 3T (Avery et al., 2014). The BNST is involved in reactive aggression, a clinically important symptom in PTSD. We hypothesized that greater resting state functional connectivity (rsFC) between the amygdala and BNST would be associated with greater irritability/aggression in PTSD.

**Methods:** 18 adults with DSM-IV PTSD, 16 trauma-exposed controls (TENC), and 25 healthy controls (HC) completed 3T MRI scanning and standardized interviews, including the Clinician Administered PTSD Scale (CAPS). rsFC was assessed in CONN 15D. A BNST mask (Avery et al., 2014) was used to place the BNST seed. ROI-to-ROI connectivity values between the amygdala and the BNST were extracted. Multivariate statistics were performed to test associations in both hemispheres, controlling for age and sex.

**Results:** Group differences in rsFC between the BNST and amygdala were not significant. However, within the PTSD group, greater CAPS irritability/aggression was associated with increased rsFC between the BNST and amygdala, F(2,13)=4.238, p = 0.038. This was driven by the left hemisphere, F(1,14) = 9.087, p = 0.009. This finding persisted after controlling for total CAPS scores.

**Conclusions:** In PTSD patients, greater irritability/aggression was associated with increased connectivity between the left BNST and left amygdala. These results highlight the possible contribution of sustained threat perception to irritability/aggression in PTSD and suggest a possible target for interventions specific to that behavioral profile.

**Supported By:** R01 (to IR)

**Keywords:** PTSD - Posttraumatic Stress Disorder, Resting state fMRI, BNST, Amygdala, Aggression

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239. Disentangling Associations between Antisocial Behavior and Anxiety Disorders with Amygdala-Orbitofrontal Functional and Structural Connectivity in Females

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**Background:** Conduct disorder (CD) and anxiety disorders (AD) are often comorbid. Both are characterized by hyperreactivity to threat, reduced functional connectivity of the amygdala-orbitofrontal cortex (OFC) circuit, and reduced structural integrity of the uncinate fasciculus. Presently, it is not known if these neural abnormalities are similar in women with a history of both CD and AD and those with only AD.

**Methods:** Three groups of women (mean age 24.7 years); CD+AD (n=23); AD not CD (n=30); neither disorder (ND, n=17); completed clinical assessments and a resting-state fMRI and Diffusion Tensor Imaging brain scan. Correlations of resting-state activity between amygdala and OFC seeds were computed. The uncinate fasciculus was reconstructed using tractography, manually dissection and tract-average axial and radial diffusivity and fractional anisotropy extracted. Groups were compared on structural and functional metrics using ANOVA and multiple regression.

**Results:** Both the CD+AD and AD groups showed reduced left uncinate axial diffusivity compared to the ND group, but importantly, did not differ from each other. These results remained after adjusting for IQ, depression, substance dependence and childhood physical maltreatment. Left uncinate axial diffusivity was significantly associated with lifetime ADs and current anxiety symptoms, but not with CD, recent aggressive behavior, or maltreatment. There were no group differences in functional connectivity; but women with a current AD displayed reduced connectivity.

**Conclusions:** Women with lifetime CD+AD and those with AD present similarly altered microstructure of the uncinate fasciculus. This abnormality may represent a mechanism common to the two disorders by which the OFC fails to down-regulate a hyperreactive amygdala.

**Supported By:** Swedish Foundation for Strategic Research; MOBilising mot narkotika; Stockholm County Council

**Keywords:** Anxiety Disorder, Conduct Disorder, white matter integrity, Fronto-limbic Connectivity, Amygdala

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240. Differences in Resting-State Functional Connectivity of Posterior and Anterior Hippocampus in Post-Traumatic Stress Disorder

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Background: Most resting-state functional connectivity (rs-FC) studies in PTSD have not examined the hippocampus as their primary seed region, while also referring to it as a singular structure, whereas research has clearly shown a dissociation between posterior and anterior hippocampal connectivity. PTSD research has also overlooked age-related differences in anterior and posterior hippocampus connectivity. Here we examined whether PTSD patients and trauma-exposed healthy controls (TEHCs) exhibit differential rs-FC of anterior and posterior hippocampus with key brain regions implicated in PTSD. We also explored the association between age and rs-FC in PTSD.

Methods: Rs-FC analysis was performed using two seed regions of interest (ROIs; anterior and posterior hippocampus) and five target ROIs (amygdala, insula, medial prefrontal cortex, posterior cingulate cortex (PCC) and precuneus) among 48 PTSD patients and 34 matched controls.

Results: A group-by-hippocampus interaction was found for the precuneus (p=0.025) and PCC (p=0.05) pathways. Post-hoc analyses revealed a pathologic loss of anterior to posterior connectivity differentiation between the hippocampus and the precuneus and the PCC in PTSD compared to controls (p<0.001 and p=0.016, respectively). The PTSD group also demonstrated a lower negative connectivity of the posterior hippocampus-precuneus pathway compared with the TEHC group (p=0.0076). Among PTSD patients, increased age had the effect of normalizing posterior hippocampus-precuneus and -PCC connectivity (r=−0.34, p=0.018; r=−0.303, p=0.036, respectively), whereas no such effect was noted for the control group.

Conclusions: PTSD is characterized by an aberrant differentiation of anterior and posterior hippocampus connectivity with the precuneus and PCC, a pattern that appears to diminish with increasing age.

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Keywords: Hippocampus, PTSD - Posttraumatic Stress Disorder, Resting state functional connectivity, Age

241. Influence of Prenatal Maternal Depression on Amygdala-Prefrontal Circuits in Infant

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Background: Prenatal exposure to maternal depression is common and puts offspring at risk for developing a range of neuropsychiatric disorders. Despite its prevalence and adverse associations, neurobiological processes by which prenatal maternal depression (PMD) confers risk remain unclear.

Methods: We assessed maternal mood and fetal behavior between 34 and 37 gestational weeks. After birth, we collected resting-state (sleep) functional magnetic resonance imaging (fMRI) and diffusion MRI in 64 infants (mean age=5.8±1.17 weeks) with (n=20) and without (n=44) in utero exposure to PMD. We investigated functional and structural connectivity within amygdala–prefrontal circuits.

Results: We found atypical amygdala–prefrontal connectivity in PMD-exposed infants. Resting fMRI indicated increased an inverse correlation between the amygdala and the dorsal prefrontal cortex (PFC), bilaterally. A sophisticated timeseries analysis using dynamic causal modeling showed, in PMD-exposed infants, a stronger excitatory influence from the amygdala to the PFC, and a weaker excitatory influence from the PFC to the amygdala, compared with controls. Diffusion tractography indicated a decreased connection strength between the right amygdala and the right ventral PFC. Last, path analyses supported a mechanistic account relating prenatal maternal depression to a third-trimester fetal behavior: PMD affects amygdala–PFC connectivity, which in turn, correlates with an increase in fetal heart rate reactivity to in utero perturbation.

Conclusions: This study suggests that the maturation and coordination of central and peripheral physiology are affected by prenatal exposure to maternal depression. It also supports the notion that PMD-associated variations in the development of amygdala–PFC circuits are relevant for future neurobehavioral maturation.

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Keywords: Maternal Depression, neonatal, Amygdala, PFC, heart rate reactivity

242. Superficial White Matter Integrity in Autism Spectrum Disorders

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Background: Autism spectrum disorders (ASD) are characterized by an atypical brain growth and abnormalities in the anatomical and functional connectivity. These abnormalities have been identified in the long-distance tracts (antero-posterior fasciculi, corpus callosum). Very few studies have explored short-distance tracts (cortico-cortical U-shaped fibers), despite their importance in the local connectivity (between adjacent cortical gyri) and in the cognitive functions. Our work aims to study short-distance anatomical connectivity in ASD subjects compared to controls.

Methods: We included thirty ASD subjects and forty male controls without mental retardation. The subjects benefited from a 3T MRI (Neurospin), with anatomical and diffusion weighted sequences. We performed a whole brain tractography (Connectomist 2.0) and automatically segmented 63 short tracts. For each fasciculus, we extracted mean gFA (generalized Fractional Anisotropy), MD (Mean Diffusivity), AD (Axial Diffusivity) and RD (Radial Diffusivity). An ANCOVA was performed with gFA.
243. Implications of Newborn Amygdala Connectivity on Fear Vs. Negative Emotionality Development over the First Year of Life

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Background: Connectivity between the amygdala, ventral medial prefrontal cortex (vmPFC) and anterior insula (al) is implicated in internalizing psychiatric disorders across the lifespan. We have previously shown connectivity patterns between these regions in newborn infants predict fear and relative levels of fear and cognitive development at 6-months-of-age. In the present study we examined the implications of these connectivity patterns for ongoing development of fear and negative emotionality across the first year of life.

Methods: Infant fear and negative emotionality were assessed at 6, 9 & 12- months of age via the Infant Behavior Questionnaire (IBQ) in 60 maternal-infant dyads. Previously identified correlations between the amygdala and al and vmPFC were examined and related to these measures of fear and emotionality (scan age=25.5+/−12.2 days). We covaried for maternal depressive symptoms, and examined maternal sensitivity and infant cognitive development as potential moderators.

Results: In line with typical development, significant growth in fear (mean slope = 0.299, p<0.001) and negative emotionality (mean slope =0.184, p<0.001) was observed from 6-12-months. Stronger newborn amygdala-al connectivity was associated with higher fear (B= 3.023, p< 0.001) at 6 months-of-age and less increase in fear over time (B= −1.089, p= 0.004). Lower newborn amygdala-vmPFC connectivity predicted an increase in negative emotionality over time (B= −0.8, p= 0.007). Neither maternal sensitivity nor infant cognitive development moderated these relationships.

Conclusions: Newborn amygdala connectivity modulates emerging differences in fear and negative emotionality over a critical, early developmental period. Understanding the role of this connectivity in these developmental trajectories has implications for identifying the etiology of internalizing symptomatology.

Supported By: NIH
Keywords: Amygdala, Fear, Resting state fMRI, Infant Temperament, development

244. Effects of Heart Rate Regressors on Functional Connectivity in ASDs

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Background: Inclusion of physiological data (i.e., heart rate [HR], respiration rate) is recommended for fMRI analyses. In children with Autism Spectrum Disorders (ASDs), physiological variables, including those associated with frequently comorbid anxiety symptoms, may impact fMRI data quality (Ming et al., 2005). We investigated whether physiological data differ in ASD compared to typically developing (TD) participants, potentially confounding intrinsic functional connectivity (iFC) analyses.

Methods: Physiological data collected during resting state fMRI scans in 60 children (ages 7-18; 30 ASD, 30 TD) were quality controlled. Group differences in mean HR (M-HR) and HR standard deviation (SD-HR) were examined, as well as relationship of these values to ASD symptom severity. IFC analyses were performed with (HR+) and without (HR−) HR regressors. Difference between HR+ and HR− iFC matrices (106 regions of interest) was calculated as mean absolute difference of functional connectivity values (M-difference).

Results: Data quality of physiological parameters was variable, resulting in a reduced final sample (n=39; ASD=19, TD=20) and exclusion of respiratory data. No significant group differences were found in M-HR, SD-HR or M-difference. Within ASD, M-HR positively correlated with repetitive behavior severity (r(16)=.51, p=.04). For all participants, IFC matrices differed between HR+ and HR− (M-difference>0, p<.001). Degree of difference in IFC correlated positively with HR (r(34)=.41, p=.02).

Conclusions: With commonly used equipment, physiological measures require careful quality control. Including HR as a nuisance regressor in iFC may impact group differences, especially in clinical populations that may show systematic differences in HR. Inclusion of physiological data without adequate quality control, however, may confound findings.

Supported By: NIH R01 MH081023, NIH K01 MH097972
Keywords: Functional connectivity, Heart Rate, ASD, fMRI, Physiology
245. Reliability of Neural Activation and Connectivity on an Implicit Face-Emotion Processing Paradigm in Youth

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Background: Face-emotion processing paradigms are often used to study pathophysiology and treatment mechanisms in psychiatric conditions, including in pediatric populations. Here, we evaluate the test-retest reliability of BOLD activation and functional connectivity on an implicit face-emotion processing paradigm in youth.

Methods: Twenty-five healthy youth (M=14.90, SD=2.64, range: 9.53-20.09, 60% female) completed two fMRI scanning sessions approximately two months apart (M=75.12 days, SD=15.12). During each fMRI scan, participants judged the gender of neutral, happy, fearful and angry face-emotions, each emotion with three intensities of expression (50%, 100%, 150%). A Bayesian method of the classic intra-class correlation (ICC) assessed reliability of BOLD activation and amygdalae seed-based functional connectivity across the two sessions. We investigated reliability evoked for all task events compared to baseline, and two sets of functional contrasts: emotion-specific contrasts and linear slopes of intensity for each emotion condition. ICC results were thresholded at voxelwise p=0.05, whole-brain cluster corrected to p<0.05 (k=75).

Results: Intra-class correlations demonstrated strong reliability in activation of the dorsolateral, medial and ventrolateral PFC, fusiform face area, and middle and inferior occipital cortex to task events compared to baseline. However, reliability of emotion-specific functional contrasts was more variable for both activation and connectivity, with significant clusters emerging for some contrasts but not for others. Linear slopes of emotion intensity generally exhibited poor test-retest reliability of both activation and connectivity.

Conclusions: While comparisons to baseline demonstrated good reliability, functional contrasts showed relatively poor reliability of activation and connectivity. These findings have implications for the selection of conditions and analytical contrasts in this task.

Supported By: ZIA MH002778

Keywords: fMRI, Emotion, emotional face processing, test-retest, Youth

246. Physical Neglect during Childhood Alters White Matter Connectivity in Healthy Young Males

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Background: Childhood adversity (CA) leads to greater vulnerability for psychopathology by causing structural as well as functional brain abnormalities. Recent findings on gray matter effects point towards the importance of identifying CA outcome as a function of different CA types, varying in the dimensions of threat and deprivation. Using diffusion tensor imaging, we investigate whether different forms of childhood adversity impact differently on white matter connectivity in a healthy cohort not confounded by other aspects of disease.

Methods: In 120 healthy young males, we assessed different forms of maltreatment during childhood with the Childhood Trauma Questionnaire (CTQ). Fractional anisotropy (FA) and mean diffusivity (MD) images were generated and projected onto a skeleton. The resulting data fed into voxelwise statistics using TBSS (Tract-Based Spatial Statistics. FA and MD were correlated with CTQ subscores.

Results: Of all CTQ-subscores, only physical neglect predicted a decrease of FA but not MD in the bilateral anterior thalamic radiation around the middle frontal gyrus and the right inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the cingulum and precuneus. Reduced FA in the posterior cingulum mediated effects of physical neglect during childhood on anxiety levels at trend level.

Conclusions: Physical neglect may have severe consequences and should be considered equally important to more active forms of abuse. FA changes, particularly in the cingulum, actually appear to a functional consequence and are linked to trait anxiety, a major transdiagnostic predictor of affective disorder. Potentially this reveals a mechanistic chain that forms one pathway from CA to disease.

Keywords: Diffusion Tensor Imaging (DTI), Childhood adversity, physical neglect, Tract-Based Spatial Statistics

247. Structural Networks Characterise Methylphenidate Treatment Response in ADHD

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Background: While methylphenidate (MPH) is largely successful in treating the symptoms and cognitive impairments associated with ADHD, in approximately 30% of cases it is either ineffective or causes intolerable side-effects. The exact biological reasons for this individual variability in MPH response are unclear. We used graph theory to determine whether whole-brain white matter connectivity differed in MPH responders versus non-responders.
Methods: Thirty-six children and adolescents with ADHD completed a 6 week MPH trial (international Study to Predict Optimized Treatment Response in ADHD; iSPOT-A). Treatment response was defined as >25% improvement from baseline on the ADHD-Rating Scale. Structural connectivity matrices were constructed using DTI probabilistic tractography between 84 parcellated whole-brain regions. Graph theory was applied to quantify global network characteristics (characteristic path length, clustering coefficient and global efficiency) and the connectivity of local nodes within the network.

Results: MPH responders (R, n=20) exhibited increased pretreatment global efficiency relative to non-responders (NR, n=16). Locally, NR had higher connectivity of the right superior temporal (p<.04) and supramarginal (p<.04) regions, while R had greater connectivity of the left caudate (p<.02) and amygdala (p<.02). Lower right supramarginal and higher left caudate connectivity were associated with greater reduction of inattentive symptoms (r=.45, p=.006; r=−.42, p=.01), while higher amygdala connectivity was associated with greater hyperactivity symptom reduction (r=−.574, p<.001).

Conclusions: Favorable clinical response to MPH may rely upon efficient network organization and heightened baseline connectivity within striatal and limbic networks. Structural connectomics provides new insights into the inter-individual variability in MPH response in child and adolescent ADHD.

Supported By: The iSPOT-A trial was sponsored by Brain Resource Company Operations Pty Ltd

Keywords: ADHD, Diffusion Tensor Imaging (DTI), Methylphenidate, graph theory, connectome

248. Neural Correlates of Frustration in Children with ADHD Compared to Typically-Developing Children

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Background: Frustration tolerance is noted to be poor in children with ADHD compared to typically-developing controls (TDC). However, little is known about the neural correlates underlying poor frustration tolerance in children with ADHD. This study examined the neural correlates of frustration in children with ADHD compared to TDCs using an adapted version of the Mirror Tracing Persistence Task (MTPT).

Methods: Participants included 52 children with DSM-5 ADHD and 33 TDCs (ages 8-17 years) who completed the MTPT in which participants trace the outline of a star using the computer mouse, but to elicit frustration, the controls are reversed and the task restarts if the participant makes an error. Participants can quit the task at any time, but are told their prize depends on task performance. Dependent variables include: latency to quit and quit/no quit. High resolution MPRAGE images were acquired. Subcortical (caudate, putamen, globus pallidus, thalamus) and cortical (dIPFC, OFC, mPFC, and ACC) volumes of interest were extracted.

Results: Results showed children with ADHD (controlling for age) had a shorter latency to quit than TD children, F(2,82)= 5.25, p <.05, suggesting poorer frustration tolerance. Smaller putamen volumes were associated with quitting the task among children with ADHD (n=36; right: r=−.450, p< .01; left: r=−.291, p=.08), whereas smaller mPFC volumes (left: r=−.382, p< .05; right: r=−.361, p=.06) and right dIPFC volume (r=−.390, p< .05) were associated with quitting the task among TDCs (n=25).

Conclusions: Results suggest distinct neural correlates of frustration in children with ADHD compared to TDCs.

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Keywords: Attention Deficit Hyperactivity Disorder, Emotion Regulation, frustration, Neuroimaging

249. Shared and Unique Neural Correlates of Threat Processing in Pediatric Irritability and Anxiety

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Background: Pediatric irritability and anxiety are highly comorbid, and both are characterized by an attention bias toward threat. We examine shared and unique neural mechanisms of threat processing in irritability and anxiety.

Methods: fMRI data were acquired from 199 youth (mean age=13.0 years; 54% female), including those with disruptive mood dysregulation disorder (n=55), anxiety disorders (n=51), attention-deficit/hyperactivity disorder (n=37), and healthy volunteers (n=56). A dot-probe attentional task assessed the impact of a threat cue (angry vs. neutral face) on neural activation and functional connectivity. All participants were assessed on levels of irritability and anxiety. Given the collinearity of these two dimensions, structural equation modeling (SEM) was used to parse shared vs. unique variance in scores.

Results: Whole-brain ANCOVAs revealed shared and unique neural correlates of irritability and anxiety. When viewing angry vs. neutral faces, higher negative affectivity (shared variance in scores) was associated with increased activation in the medial dorsal nucleus of the thalamus (p<.005, whole-brain corrected). When the dot-probe followed the neutral vs. angry face, higher irritability was associated with increased activation in the bilateral striatum and inferior parietal lobule, and right insula and dIPFC (all p<.005, whole-brain corrected). In contrast, higher anxiety was associated with decreased connectivity of the amygdala and inferior frontal gyrus with the cingulate gyrus (all p<.005, whole-brain corrected).
Conclusions: This unpublished study used SEM to parse comorbid symptom dimensions, to better understand their shared and unique neural correlates. Indeed, individual differences in neural activation were largely driven by irritability, whereas differences in neural connectivity were driven by anxiety.

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Keywords: Irritability, Anxiety, pediatric, Functional MRI, Structural Equation Modeling

250. ADHD Symptoms in Youth Are Differentially Associated with Polygenetic Risk and Neural Substrates if There is a History of Traumatic Brain Injury

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Background: Attention Deficit/Hyperactivity Disorder (ADHD) is a major sequela of traumatic brain injury (TBI) in youth. The objective of this study was to examine whether genetic risk for ADHD and altered brain structure; differentially predict ADHD symptoms in youth with and without history of TBI.

Methods: In a community sample of youth, we investigated whether having a history of TBI modulates the association between ADHD symptoms and 1. Polygenetic risk for ADHD (TBI=333, NoTBI=2135) 2. Volumes of basal ganglia structures associated with ADHD (TBI=134, NoTBI=719) 3. Fractional anisotropy (FA) of white matter tracts associated with axonal injury following TBI (TBI=87, NoTBI=419).

Results: Youth with a history of TBI reported an increased number of ADHD symptoms compared to those without history of TBI. Polygenic risk was associated with ADHD in those without a history of TBI but not in youth with history of TBI. Globus Pallidus volume was not associated with ADHD symptoms in youth without TBI but was negatively associated with symptoms in youth with TBI. Striatum volume was negatively associated with the number ADHD symptoms in both groups. FA in the genu of the corpus callosum, and MD in the corona radiata, showed opposite direction of association with ADHD symptoms in youth with and without history of TBI.

Conclusions: These results suggest that ADHD associated with TBI is a result of mechanical insult to similar neural pathways that have distinct and similar effects from those affected by genetic risk in developmental ADHD.

Supported By: SickKids Foundation and FedEx Catalyst Scholarship

Keywords: TBI, Diffusion Tensor Imaging (DTI), Polygenic Risk Score, ADHD

251. Diverging Cognitive Trajectories in Pediatric Moderate to Severe Traumatic Brain Injury

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Background: Traumatic brain injury (TBI) is the leading cause of death and disability in children worldwide, and patients with TBI are at a higher risk for psychiatric disorders [1]. A single TBI can trigger pathways involved in neuronal degeneration and also cause a decline in cognitive abilities [2,3]. This may be detrimental to the developing brain, as myelin development and brain maturation continue past the age of 30 [4]. Following TBI, abnormalities in brain structure typically persist for years – and may interact with maturational processes in the adolescent brain [5].

Methods: We used diffusion weighted imaging (DWI) to non-invasively examine the white matter (WM) microstructure of the brain. We examined 21 children with moderate/severe TBI (mTBI) 1-5 months post injury (post-acute), and at a follow-up 13-19 months later (at the chronic stage). To investigate neurological outcome, we measured their interhemispheric transfer time (IHTT) using event-related potentials (ERPs), and tested its association with our DWI measures.

Results: We found that around half the TBI patients we assessed had significantly slower IHTTs at the first time point (TBI-slow), while the other half had normal IHTTs that did not differ significantly from controls in either post-acute or chronic phases (TBI-normal). In addition to reductions in fractional anisotropy (FA) in the TBI group, we found the TBI-slow group to have significant reductions in FA and increases in mean and radial diffusivity measures in the first year post injury.

Conclusions: Our results suggest a diverging neurological trajectory in the outcomes of these groups of patients.

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Keywords: Diffusion Tensor Imaging (DTI), Traumatic Brain Injury, Neurodevelopmental trajectories, children and adolescence, MRI brain imaging

252. Visceral Fat and Insular Networks: Implications on Food Craving

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1, Raquel Vilar-López2, Juan F Navas2, Cristina Martín-Pérez2, Carles Soriano-Mas1, and Antonio Verdejo-Garcia3
Background: Recent evidence reports flexible and inflexible responses of the middle and rostral insula to food-cues according to the body-homeostatic state, respectively. Studies have associated visceral fat with alterations of the insula networks, along with its effects on food craving. This study investigates how visceral fat levels modulate middle and rostral insula networks, along with its effects on food craving.

Methods: Eighty-one healthy individuals (BMI range = 19-38.3) underwent a resting-state imaging session. Visceral fat (VF) was measured using TANITA BC-420 and food craving with subjective ratings to high-calorie food-cues previously tasted. Full-factorial models in SPM12 were used to assess for linear and curvilinear associations between VF and the seed-based functional connectivity of the rostral (rIns) and middle insula (mIns), controlling for BMI. Regression analyses then assessed whether the VF-associated insula connectivity networks predicted food craving.

Results: Higher VF levels associated linearly with decreased connectivity between the mIns and subcortical regions (ventral caudate, hypothalamus, bed nucleus), and with increased connectivity between the rIns and ventromedial frontal regions (rostromedial prefrontal cortex, lateral orbitofrontal cortex-operculum). A U-shape association between the connectivity of the mIns and the primary somatosensory area (S1) of the aIns and the pons also emerged; individuals with intermediate VF levels had a reduced connectivity in this brain circuit. Food craving was associated with the decreased connectivity between the aIns and the hypothalamus and with the increased connectivity between the aIns and the ventromedial frontal regions.

Conclusions: Alterations in the connectivity of middle and rostral insula networks driven by VF levels may underlie the compromised sensitivity to homeostatic-driven eating behaviors.

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Keywords: Functional connectivity, Obesity, Body mass index, Food-craving, Interoception

253. Functional Connectome Networks Underlying Outcomes of Antidepressant Medication in Major Depressive Disorders

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Background: Antidepressant medications (ADM) remain the first-line treatment for major depressive disorders (MDD). However, the neural mechanisms through which ADM treatments work remain poorly understood. Connectomics allows a comprehensive description of brain network architecture and provides a novel framework to understand ADM mechanisms. This study used connectomics to identify resting functional brain networks that underlie remission to ADMs.

Methods: 157 MDD participants underwent fMRIs at baseline and following 8-week course of randomized treatment with either escitalopram, sertraline or venlafaxine-ER. A score at week 8 of 0 or less on the 17-item Hamilton Rating Scale for Depression defined remission. 62 age- and gender-matched healthy participants also completed fMRIs at the two time points. Inter-regional resting functional connectome matrices were mapped using AAL atlas. Network based statistical analyses were used to assess differences in pre-treatment functional connectomes between the remitter and non-remitter MDD participants. Significant sub-networks were assessed for changes post-treatment, relative to controls and as a function of ADM type.

Results: Greater intra- and inter-network connectivity of the default mode network (DMN) with other intrinsic brain functional networks characterized remitters from non-remitters irrespective of ADM type. This comparatively greater connectivity in remitters persisted post-treatment and did not differ at baseline from healthy connectivity. By contrast, the hypo-connectivity of non-remitters distinguished them from controls at baseline but lessened over 8 weeks despite the lack of symptom remission.

Conclusions: Preserved resting functional connectivity of the DMN and its interaction with executive brain intrinsic networks may characterize acute recovery with ADMs in depression.

Supported By: Brain Resource Ltd

Keywords: connectome, Major Depressive Disorder (MDD), Resting state functional connectivity, antidepressant medication, Remission

254. Novel Transcriptome-Based Polygenic Risk Score for Depression is Associated with Reduced dIPFC Efficiency and Disrupted Structural Covariance Network Properties

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Background: Neuroimaging has associated depression with dysfunction of the dorsolateral prefrontal cortex (dIPFC) likely reflecting impoverished top-down regulation of emotion. Parallel work in human postmortem brain has identified depression-related transcriptomic changes in the dIPFC.
To bridge these lines of research we sought to map a transcriptome-based polygenic risk score (PRS) onto MRI-assessed dIPFC function and whole-brain structural covariance network properties.

**Methods:** Using the GTEx database, we developed a PRS based on 243 common cis-eQTL SNPs which bias gene expression in the dIPFC towards a depression-like molecular phenotype. We next examined the effect of this PRS on dIPFC activity during a working memory task (n=183) in the Duke Neurogenetics Study. We further conducted a structural covariance network analysis (n=1063) to probe potentially development-mediated PRS effects on dIPFC network hub status, as well as whole-brain network clustering (transitivity) and integration capacity (mean path length).

**Results:** Higher PRS was associated with greater left dIPFC activity in the absence of performance differences during a working memory task, but only in participants reporting high childhood trauma (p =0.03). Structural covariance analyses revealed higher PRS was independently associated with decreased left dIPFC “hubness” and increased mean network path length.

**Conclusions:** Our results suggest a depression-like transcriptome polygenic risk score is associated with inefficient dIPFC activity supporting working memory, particularly in individuals exposed to early life stress. The same molecular phenotype may also disrupt developmentally mediated shared structural plasticity between the dIPFC and other regions, leading to long-term whole-brain network reorganization consistent with reduced integration capacity.

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**Keywords:** Depression, Working memory, DLPFC, Polygenic Risk Score, Brain networks

255. Greater Gyrification of the Inferior Frontal Gyrus as a Marker of Genetic Risk for Bipolar Disorders

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**Background:** In our previous genetic high-risk study, we found replicated evidence for a larger right inferior frontal gyrus (rIFG) gray matter volume in both unaffected as well as affected relatives of bipolar probands relative to controls. Structural changes in the rIFG are one of the few replicated biomarkers of familial predisposition to BD. Here we examined gyrification of the IFG in affected and unaffected relatives of BD probands.

**Methods:** We measured local gyrification index (LGI) using FreeSurfer. LGI is an automated 3-dimensional metric that quantifies the amount of cortex buried within the sulcal folds versus the outer visible cortex. LGI was compared between 38 unaffected, 28 affected relatives of BD probands, and 41 age matched controls.

**Results:** Multivariate analysis of variance (MANOVA) revealed a significant group difference in the folding (p = 0.02) of the rIFG. The largest between-group gyration differences were localized to pars opercularis and pars orbitalis of the rIFG, where in all instances we observed the largest gyration in unaffected participants at genetic risk for BD.

**Conclusions:** The finding of increased gyration in those at risk for BP replicates our prior work in a larger sample using a different method of analysis. Measures of gyration provide a complementary anatomical marker to assist in the understanding of abnormal neurodevelopmental processes in BD.

**Supported By:** CIHR; NSHRF

**Keywords:** bipolar disorder, inferior frontal gyrus, neuroimaging, gyrification, genetic risk

256. Hippocampal Tissue Properties, as Evaluated by Flair and Susceptibility Weighted Imaging in a Preliminary Sample of Patients Treated with ECT

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**Background:** Electroconvulsive therapy is an effective acute treatment of major depressive episodes. Volumetric increases of the hippocampus and other brain areas have been demonstrated after ECT by using MR imaging. Though harmful effects have not been identified, the structural changes have not been characterized by susceptibility weighted imaging (SWI) or Fluid Attenuated Inversion Recovery (FLAIR), MR sequences in common clinical use which are sensitive to tissue parameters found in microbleeds and oedema, respectively.

**Methods:** Patients in a major depressive episode referred for ECT (n=15) were scanned before and after ended treatment, and a group of healthy controls (n=8) were scanned twice at corresponding time intervals. Structural T1 volumes were segmented using FreeSurfer (V5.3.0). SWI and FLAIR volumes were registered to the T1 volume, and the accuracy confirmed by visual inspection. Mean voxel intensity values in the hippocampus, as segmented by FreeSurfer was then obtained for SWI and FLAIR.

**Results:** Intensity differences between the two scans were calculated for the hippocampus for each hemisphere. Data was evaluated for normality through Shapiro-Wilk test, and
longitudinal changes in the hippocampus were compared between groups by independent t-test as well as Cohen’s d: FLAIR; right p=0.12 d = −0.44, left p=0.8 d = −0.21 and SWI; right p=0.6 d = −0.16, left p=0.7 d = −0.22. **Conclusions:** Volume increase of the hippocampus is known to be associated with ECT. We did not find corresponding changes in hippocampal tissue properties on FLAIR and SWI. Our sample size is limited, and the results should be confirmed in larger samples. **Supported By:** Western Norway Regional Health Authority, Haukeland; University Hospital and the University of Bergen, Norway. **Keywords:** MRI brain imaging, Electroconvulsive therapy (ECT), Hippocampus

### 257. Effects of Electroconvulsive Therapy on Amygdala Function in Major Depression — A Longitudinal fMRI Study

**Ronny Redlich, Katharina Dohm, Dario Zaremba, Christian Bürger, and Udo Dannlowski**

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**Background:** Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depression. However, little is known regarding brain functional processes mediating ECT effects.

**Methods:** In a non-randomized prospective study, fMRI data during the automatic processing of subliminally presented emotional faces were obtained twice, about six weeks apart in patients with major depressive disorder (MDD) before and after treatment with ECT (ECT, n=24). Additionally, a control sample of MDD-patients treated solely with pharmacotherapy (MED, n=23), and a healthy control sample (HC, n=22) were obtained.

**Results:** Before therapy, both patient groups equally showed elevated amygdala reactivity to sad faces compared to HC. After treatment, a decrease in amygdala activity to negative stimuli was discerned in both patient samples indicating a normalization of amygdala function, suggesting mechanisms potentially unspecific for ECT. Moreover, a decrease in amygdala activity to sad faces was associated with symptomatic improvements in the ECT sample (rspearman=−.48, P=.044), and by tendency also for the MED sample (rspearman=−.38, P=.098). However, we did not find any significant association between pre-treatment amygdala function to emotional stimuli and individual symptom improvement, neither for the ECT sample, nor for the MED sample.

**Conclusions:** In sum, the present study provides first results regarding functional changes in emotion processing due to ECT treatment using a longitudinal design, thus validating and extending our knowledge gained from previous treatment studies. Limitation: ECT patients received concurrent medication treatment. **Supported By:** RE111604 to RR **Keywords:** Electroconvulsive therapy (ECT), Affective Disorders, Treatment Response, Longitudinal Brain Imaging, Amygdala

### 258. The Effect of Clinical Course on Longitudinal Changes in Hippocampal Volume: A 2-Year Follow-Up Study in Patients with Major Depressive Disorder

**Katharina Dohm, Dario Zaremba, Ronny Redlich, Dominik Grotegerd, and Udo Dannlowski**

Department of Psychiatry, University of Münster

**Background:** Structural brain alterations in major depressive disorder are well studied in cross-sectional designs, but little is known about the causality between onset and course of depression, as well as neurobiological changes over time. To explore the direction of causality, longitudinal studies with a long time window are needed, but only few have been undertaken so far. In the present study we explored the effect of the clinical course during a two year interval on changes in hippocampal volume.

**Methods:** In a longitudinal design we examined 55 patients with DSM-IV major depressive disorder at baseline and after two years using high-resolution magnetic resonance imaging (MRT). Gray matter (GM) volumes have been analyzed by Computational Anatomy Toolbox (CAT12) for SPM12. A 2(time)x2(group) ANOVA was conducted using the hippocampus as ROI. Depending on the clinical course during the follow-up interval, we divided patients into two groups: patients suffering from further depressive episodes and patients with no episodes during baseline and follow-up.

**Results:** There was a significant interaction effect between time and group in the right hippocampus (x,y,z=14, -8, -18; T(104)=3.77; p<0.0001; k=161 voxels) resulting from an increase in GM volume in the group with no episodes during follow-up and a trend of decrease of GM volume in the group with further episodes.

**Conclusions:** The results suggest that depressive episodes have a neurotoxic effect on hippocampal volume (neurotoxicity hypothesis). Symptom-free periods seem to be neuroprotective or neuroregenerative, potentially mediated by a medication effect. **Supported By:** The study was supported by grants from the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]; grant FOR 2107; DA1151/5-1 to Udo Dannlowski) **Keywords:** Longitudinal Brain Imaging, Major Depressive Disorder (MDD)

### 259. NIRS Observation of Changes in Brain Activity following Low Field Magnetic Stimulation

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McLean Hospital

**Background:** Low Field Magnetic Stimulation (LFMS) is a novel electromagnetic treatment for depression. LFMS acts immediately on depressed states but does not alter mood in those without depression. To understand and develop the treatment, studies of physiologic change in response to LFMS are needed. **Methods:** Nine healthy controls were recruited to participate in this randomized, sham controlled, single blinded study. Subjects received either active or sham LFMS on two
separate occasions within two weeks. Subjects were fitted with a 12 optode cap providing 9 channels of data in bilateral prefrontal regions. An additional infrared plethysmograph was placed on the left forefinger for use in the removal of physiologic confounds. Data were then acquired in the resting state for 5 minutes, followed by LFMS (active or sham) for 20 minutes, and in the resting state for 5 additional minutes. Standard artifact detection and timeseries analysis were performed to detect post-pre change in absolute deoxy- and oxy-hemoglobin levels for all channels as a global measure of change. Repeated measures ANOVA was used, within the FSL software package, to provide a group result.

**Results:** We observed a significant decrease in global deoxy-hemoglobin concentration (−0.44 ± 0.25 μM, p < 0.04) and a corresponding, trending, increase in oxy-hemoglobin concentration (+1.08 ± 0.75 μM, p < 0.8) associated with LFMS.

**Conclusions:** The electric fields that LFMS induces have a global cortical distribution. We hypothesize that this global stimulation results in regional changes in neuronal activity. Interestingly, these results indicate a reduction in cortical [HB] which may indicate a reduction in neuronal activity.

**Supported By:** Shervert Frazier Foundation, Tal Medical Inc.

**Keywords:** NIRS, LFMS, Mood Disorders, Stimulation

### 260. Processing of Social and Monetary Gains and Losses: Evidence for Common and Distinct Neural Correlates

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**Background:** Impairments in processing rewards and losses are present in several psychiatric disorders, such as depression, bipolar disorder and schizophrenia. Whereas most studies examine monetary gains and losses, it is likely that social “gains” and “losses” also play an important role in the development and maintenance of these disorders. This study investigated the neural correlates of reward and loss, both social and monetary, in healthy controls.

**Methods:** A preliminary sample of 6 participants [(mean age(SD): 20 years(1.67)] completed two fMRI tasks: the Social Feedback and the Monetary Feedback tasks, which provided feedback on romantic rejection/acceptance, and monetary wins/losses, respectively. A priori regions of interest included the bilateral nucleus accumbens, amygdala, anterior insula, dorsal anterior cingulate, thalamus and dorsal striatum. Voxel-wise analyses were performed (PFWE < 0.05), and regions that survived a height threshold of Puncorrected < 0.001 are also reported.

**Results:** The dorsal striatum showed a trend for activation during both social acceptance (Puncorrected = 0.001) and monetary reward (Puncorrected = 0.001) (vs neutral). The left amygdala was significantly activated during both social acceptance (t = 3.73; PFWE = 0.03) and rejection (PFWE = 0.05) (minus resting baseline). Presentation of monetary reward was uniquely associated with a trend for activation in the right thalamus (Puncorrected < 0.001) (minus baseline).

**Conclusions:** These preliminary results highlight common neural responses in the dorsal striatum, in response to social and monetary gain. Distinct activations in the thalamus during monetary gain, and in the amygdala during rejection suggest dissociable neural responses. These results highlight the importance of examining gains/losses in both monetary and social contexts, particularly in disorders sensitive to the social environment.

**Supported By:** R01 MH102264 (Hsu)

**Keywords:** fMRI, Monetary Gain, Monetary Loss, Social Acceptance, Social Rejection

### 261. Assessing Pretreatment Multimodal Neuroimaging Markers of Lithium Treatment Response in Bipolar Depression

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**Background:** Lithium remains the first line therapy for bipolar disorder (BD), despite low response rates and high risk of side effects. No criteria predictive of an individual’s responsiveness are used clinically. We present preliminary, multimodal neuroimaging findings showing an association between baseline measurements and lithium-treatment outcome.

**Methods:** We performed [11C]-CUMI-101 PET and MRI scans on 13 BD patients before lithium treatment. CUMI was used to quantify serotonin-1A autoreceptor (5HT1A) binding. MRI metrics included resting-state fMRI (rsfMRI) arterial spin labeling (ASL) and diffusion tensor imaging (DTI). Regions examined included the dorsal raphe, amygdala, temporal pole (TP) and prefrontal cortex (PFC). Baseline imaging findings were correlated to changes in symptom severity as reflected by Hamilton Depression Rating Scale (HDRS). Spearman’s rank correlation analysis was performed, reported as r, rank and P, rank.

**Results:** PET: Lower 5HT1A binding potential in the raphe correlated with better outcome, reflected by a greater reduction in HDRS (r, rank = 0.68; P, rank = 0.04). A trend was observed in TP-PFC connectivity (r, rank = −0.45; P, rank = 0.18). Higher pretreatment connectivity was linked to better outcome. ASL: A trend between blood flow to the TP and treatment outcome was observed (r, rank = 0.5; P, rank = 0.17), with lower blood flow associated with better outcome. rsfMRI: A trend between TP-amygdala functional connectivity and treatment outcome was observed (r, rank = −0.88; P, rank = 0.07). Higher connectivity was associated better outcome. When DTI, ASL, PET measures were combined, r, rank was further improved to 0.91.

**Conclusions:** Although few of these metrics attained statistical significance due to the small sample size, this work establishes the possible usefulness of a portfolio of baseline neuroimaging measurements in determining patient-specific lithium response.
262. Ketamine’s Effects on Brain Function during Emotional Processing in Major Depressive Disorder
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Background: In major depressive disorder (MDD), there is a need for rapidly acting pharmacological treatments. Recent studies showed that ketamine, a glutamatergic modulator, can have antidepressant effects within hours. To study its mechanism of action in the brain as related to affective processing in depression, we investigated the effects of ketamine on fMRI activation during an emotion evaluation task.

Methods: In a double-blind placebo-controlled crossover study, 30 (unmedicated) patients with treatment-resistant MDD and 16 healthy volunteers participated in fMRI scanning two days after an infusion of ketamine (0.5 mg/kg) or placebo. We used a 3T scanner to measure BOLD signal during an emotion evaluation task, in which faces with emotional expressions were randomly presented. In one block, participants identified the emotion as positive or negative, and in the other, identified gender. Imaging data were processed to generate individual statistical maps, which were used in a linear mixed-effect whole-brain analysis.

Results: We found a drug-by-block interaction in clusters in frontal and temporal regions, anterior/posterior cingulate, and left parahippocampal gyrus (FWE-corrected p<0.01). This interaction was driven by greater BOLD response in MDD patients compared to healthy volunteers (who showed deactivation) during the placebo condition, along with deactivation in patients (and greater activation in healthy participants) after ketamine.

Conclusions: These results showed that during emotional processing, patients with MDD had overactivation across numerous brain regions. Following ketamine, MDD participants had an attenuated response, which resembled the response in healthy volunteers during placebo. This suggests that ketamine may have a normalizing effect on affective brain function in depression.

Supported By: NIMH Intramural Research Program
Keywords: Depression, fMRI, Ketamine, Emotional processing

263. Beta Power in Magnetoencephalography as a Potential Neurobiological Marker for Risk of Suicide in Depressed Patients
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Background: There are currently no magnetoencephalography (MEG) studies investigating suicidal ideation or behavior. Additionally, there is a gap in the literature on the biological underpinnings of suicidal ideation, especially among actively suicidal depressed patients. Neurobiological risks factor for suicide suggest future efforts could target suicide risk trajectories (Lipard, Johnston, & Blumberg, 2014). The current study looks at resting spectral power, measured via MEG, as a potential neural correlate for suicidal ideation.

Methods: Un-medicated subjects (N=30, age=36±10.60% female) meeting MDD criteria underwent 250s resting state MEG recordings, acquired on a 275 channel CTF system. The degree of suicidal ideation was measured using item 29 (scored from a scale of 1-6) on the MADRS. The mean power spectrum across 5-10 15 second artifact free epochs for 10 different sensor groups was calculated. Total power within canonical frequency bands (alpha, beta, delta, theta, gamma and high gamma) was calculated. Log transformed mean power across sensors was correlated with suicidality. For bands showing significance, further correlations were calculated within each anatomical sensor grouping.

Results: Mean power across all sensors was significantly correlated with suicidality in the beta band (R=−48, p=0.012). Further analysis of the sensor groups revealed significant correlations in left and right frontal/central sensors (p<0.01). Beta power was greatest in subjects who showed the lowest levels of suicidal ideation.

Conclusions: This preliminary analysis showing correlations between beta power and suicidality in frontal and central regions could lead to a biomarker for suicide risk in depressed patients. Future studies will investigate the anatomical localization of these correlations, as well as the effects of treatment.

Supported By: NIH
Keywords: Magnetoencephalography, Suicide risk factors, predictive biomarkers, Major Depressive Disorder (MDD)

264. Spectroscopy MRI Brain Myoinositol Changes with Oral Inositol in Depressive Bipolar Patients Treated with Lithium
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Background: There are few published studies with proton magnetic resonance spectroscopy (1H-MRS) to identify the effects of oral inositol on myo-inositol (MI) concentrations in bipolar I depression.

Methods: Seven adult patients with bipolar I current episode depressed (N=7), under treatment with lithium carbonate (within therapeutic serum levels) received open-label oral inositol 4 to 12 gr/day. No other treatments were allowed. The MI concentration in the medial and lateral prefrontal areas, fronto-orbital areas, insula, basal ganglia, thalamus and temporal and occipital cortex were measure before and after 30 days of inositol treatment. Changes in MI concentration were analyzed with 1H-MRS over time. MI was normalized with respect to the peak of creatinine (Cr) (MI/Cr ratio).

Results: A statistically significant changes were observed for MI concentration in left anterior cingular cortex (increased) (p<0.0001) and right thalamus (decreased) (p=0.016) after 30 days of treatment with oral inositol (mean
Thursday Abstracts

265. Morphometric Correlates of Depressive and Hypomanic Symptoms in Major Depression
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**Background:** Many studies have suggested that depression and bipolarity lie on a continuum within affective disorders, ranging from mild to severe symptoms in each symptom dimension, and that understanding the differential basis of these symptoms in the brain will be important in improving outcomes in the clinic. However, there is presently little research into the neurobiological substrates of depression and hypomania as dimensional constructs, and this has limited progress in this area. Our aim in this study was to identify a structural basis of these symptom dimensions in the brain.

**Methods:** We used voxel-based morphometry derived estimates of grey matter volume, to predict clinician-rated depressive symptoms and self-reported bipolarity in a sample of 47 medication-free unipolar individuals with and bipolar depression.

**Results:** We identified a pattern of grey matter volume changes that predicted depressive symptom severity accurately at an individual level. Regions with the strongest predictive weights included medial prefrontal cortex and insula, regions that we have previously shown to exhibit similar patterns of grey matter volume reduction in major depression and were not able to predict bipolarity with a similar accuracy.

**Conclusions:** Our results provide evidence of dimensional overlap in depression and bipolar symptoms having a consistent biological basis in the brain across unipolar and bipolar disorders, hinting at future directions more biomarker development.

**Supported By:** Academy of Medical Sciences, National Institute for Health Research

**Keywords:** Depression, Bipolar, Brain Imaging, Machine learning

266. Use of Miniature Fluorescence Microscopes to Investigate Place Cell Ensemble Dysfunction in a Mouse Model of Chronic Stress

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**Background:** Chronic stress can lead to clinical depression, yet little is known about the underlying neuronal circuit dysfunctions in complex mental disorders. The hippocampus, a structure essential for spatial navigation and memory, undergoes anatomical and functional changes during chronic stress. Here we utilize in vivo calcium imaging techniques in chronically stressed animals to measure how place cell function in the hippocampus is disrupted.

**Methods:** To model physiological conditions of chronic stress, transgenic mice expressing the genetically encoded calcium indicator GCaMP6f are administered daily with 400 μg/ml of hydrocortisone (CORT). Mice are implanted with miniature microscopes and are trained to run on a linear track while calcium event activity is recorded from hippocampal ensembles over several days.

**Results:** We find that long-term dynamics of place field coherence are perturbed in CORT-treated mice. Although the spatial information content of place cells is preserved, CORT-treated mice have fewer place cells that encode a significant amount of spatial information, and place field stability degrades sooner compared to untreated mice.

**Conclusions:** Chronic stress reduces the number of place cells that encode information about the location of the animal and disrupts long-term stability of their place fields. This ensemble dysfunction indicates that chronic stress impacts the ability of the hippocampus to encode neural representations and memories of the animal’s spatial location, a function pivotal to forming an accurate navigational map of the animal’s external environment.

**Supported By:** Janssen Research & Development, LLC

**Keywords:** Janssen Research & Development, LLC

267. Effects of Elevated Altitude on Bioenergetics of Cerebral Cortex in Bipolar Disorder and Healthy Subjects: 31 Phosphorus Magnetic Resonance Spectroscopic (MRS) Study

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**Background:** Increased altitude may be a risk factor for several psychiatric disorders including suicide. Oxidative stress following exposure to the hypobaric hypoxia associated with elevated altitude may increase the vulnerability of those with or at risk for bipolar disorder. In this study, we evaluated the...
Methods: Thirty-six veterans with bipolar disorder and 31 healthy veterans were recruited in Belmont, MA (N=20) and Salt Lake City, UT (N=47). Levels of Phosphocreatine (PCr), β-nucleoside triphosphate (NTP), inorganic phosphate (Pi) and pH were measured in the anterior cingulate (ACC) and posterior occipital cortices (POC) using 31-phosphorus MRS. Analysis of covariance including age as a covariate was used to evaluate the effects of altitude and bipolar disorder on cerebral bioenergetics.

Results: A main effects analysis showed there were significantly lower jNTP/total phosphate (TP) (p < 0.008), greater PCr/TP (p < 0.007) of both ACC and POC, and greater Pi/TP (p < 0.001) of POC in the subjects from Salt Lake City, altitude 4,700 feet, relative to Belmont, altitude 44 feet. A lower pH of POC in bipolar disorder subjects was also observed relative to healthy subjects (p = 0.0281). No interaction effect was observed between altitude and bipolar disorder.

Conclusions: The present findings suggest that hypobaric hypoxia may result in the abnormal cortical bioenergetics in both bipolar disorder and healthy subjects. Reactive oxygen species produced under hypobaric hypoxia may decrease the activity of creatine kinase, which would cause abnormal cerebral bioenergetics.

Supported By: VA Merit Review Grant

Keywords: Magnetic Resonance Spectroscopy, Oxidative Stress, Altitude, Bipolar Disorder, Bioenergetics

268. Longitudinal Changes and Recovery in Cortical Thickness of Collegiate Football Players

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Background: Previous studies have reported that participation in collegiate football is associated with high rates of concussion and injury. Concussion and head impact rates have been shown to be higher during game season than pre-season; however, considerable debate exists regarding the neural effects of injury during game season. This longitudinal study investigated cortical thickness changes during pre-season and post-season in collegiate football players.

Methods: Thirty members of an NCAA Division 1 football team completed an MRI protocol at the 1st pre-season (N=30. Baseline), post-season (N=23. Follow-up 1), and 2nd pre-season (N=15. Follow-up 2). T1-weighted images were acquired on a 3T Verio and processed using FreeSurfer 5.3.0. for cortical thickness calculation. Linear mixed effects modeling applied to the mass-univariate was used to analyze longitudinal changes in cortical thickness. The results were corrected using the two-stage false discovery rate method.

Results: Cortical thickness of the bilateral superior frontal, bilateral superior parietal, left lateral occipital, inferior parietal, left inferior parietal, and left posterior cingulate regions showed significant quadratic changes with time from baseline (clusters on left hemisphere β=.02, z=6.79, p<0.001; clusters on right hemisphere β=.01, t=5.10, p<0.001). No significant linear change of cortical thickness with time was found.

Conclusions: These results showed that regional cortical thickness decreased from pre-season to post-season and recovered by the following pre-season, suggesting that football game season activity may induce reversible structural brain changes. Additional studies are needed to identify the source of the reversible brain changes and to examine the impact of number and severity of injuries on recovery.

Supported By: USTAR

Keywords: Cortical Thickness, Longitudinal, Head Impacts, Collegiate Football Players

269. Assessment of White Matter Abnormalities in Cingulate Fasciculus through Diffusion Tensor Imaging in Patients with Schizophrenia with Auditory Hallucinations

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Background: Persistent auditory hallucinations (AH) in psychotic patients interfere with their functioning. The results of neuroimaging studies in AH have been conflicting. White matter abnormalities are one of the most consistently reported neuroimaging findings in schizophrenia. Diffusion tensor imaging (DTI) may be useful imaging biomarker for the exploration of white matter microstructural changes.

Methods: Thirty patients diagnosed with schizophrenia (according to DSM-5) with current as well as lifetime history of auditory verbal hallucinations were compared to 30 healthy controls. All subjects underwent DTI within one week of assessment. FA values were calculated for cingulate fasciculus using DTI studio v3.0.

Results: Two groups were comparable in terms of age, gender, education, religion, and tobacco use. Only cingulate gyrus of left cingulate fasciculus had significantly lower FA value in patient group. No significant differences were seen in FA values of right cingulate fasciculus of both the groups, nor in the hippocampal part of left cingulate gyrus. The FA values in patients did not have significant correlation with severity of SAPS or PSYRATS-H score except for positive correlation of SAPS with FA value in cingulate gyrus part of left cingulate fasciculus.

Conclusions: Reduction in FA value is associated with reduced myelination or loss of neuronal integrity. The proposed hypothesis of demyelination in schizophrenia has been supported by findings of abnormal or reduced oligodendrocytes (neuroglia responsible for creating myelin sheath). Further exploration is needed to establish findings to be illness related or hallucinations specific.
Keywords: structural neuroimaging, Schizophrenia, Diffusion Tensor Imaging (DTI), Auditory Hallucination

270. White Matter Microstructure and Cognition in Early Schizophrenia

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Background: White matter (WM) alterations have been characterised in schizophrenia. In this study we aim to delineate WM alterations and their association with cognition in the early stages of the disorder. This sample is part of an on-going, longitudinal treatment project, examining neurological changes during cognitive remediation therapy. We are reporting baseline results for biological markers to later assess during treatment.

Methods: We analyzed DTI data from 18 controls and 40 schizophrenia patients (diagnosis < 8 years). Mean age=25.02 years (SD=4.41) and 39 males.: Fractional anisotropy (FA) maps were analysed using ENIGMA-DTI protocols. FA for six WM regions of interest were extracted. A MANCOVA model was used to test for case/control FA differences, covarying for age and sex. Partial correlations between FA, MATRICS Battery and The Awareness of Social Inference Test (TASIT) were conducted.

Results: No significant case/control differences were observed for FA. For patients, positive correlations between FA and verbal learning were observed in the anterior limb of internal capsule (ALIC (R=0.45; p=0.01)) and splenium of corpus callosum (R=0.38, p=0.034). A positive correlation was observed between FA of the ALIC and TASIT (R=0.38, p=0.019). Results did not survive Bonferroni correction.

Conclusions: We observed no significant case/controls differences in FA. As data collection is ongoing, future analyses may be better powered to detect WM differences. The strongest association for FA and cognition was observed in the ALIC that connects the thalamus and frontal cortex. Future analyses of this data may help to identify regions of WM that are susceptible to change during cognitive therapy.

Supported By: NIMH RO1 MH 92440

Keywords: Schizophrenia, Cognitive Remediation, Diffusion Tensor Imaging (DTI), Neurocognition, Social Cognition

271. Negative Symptoms of Schizophrenia and Fronto-Parietal Circuit Dysfunction

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Background: In patients with chronic psychotic disorders, the severity of ‘negative symptoms’ of schizophrenia (e.g. apathy, social withdrawal, and amotivation) is the strongest predictor of functional outcomes such as employment and educational attainment. Existing antipsychotic medications are not effective in ameliorating these symptoms. Despite the significant impact of these symptoms, and the lack of pharmacologic interventions, our understanding of their pathophysiology is limited. We sought to better understand how these symptoms are related to neural circuit dysfunction.

Methods: We sought to understand how negative symptoms of schizophrenia are reflected in spontaneous brain network dynamics. We clinically characterized and collected ‘resting state’ functional Magnetic Resonance Imaging scans from a cohort of 71 subjects with schizophrenia or schizoaffective disorder. We applied a data-driven approach to these data using Multivariate Distance Matrix Regression (MDMR) to identify brain regions whose connectivity varies with the severity of negative symptoms as measured by the PANSS.

Results: This analysis revealed that dysconnectivity between the frontal (BA10) and parietal cortices strongly correlated (P<.0001) with negative symptom severity. This correlation remained highly significant despite correction for movement and medication effects. This dysconnectivity was not related to the severity of positive symptoms of schizophrenia or mood symptoms.

Conclusions: Here we demonstrate that dysconnectivity in large scale fronto-parietal networks is associated with the severity negative symptoms of schizophrenia. This finding does not appear to be related to other symptoms of psychosis or mood disorders. The localization of the anatomical deficit is consistent with substantial literature implicating frontal pole lesions with amotivation and apathy.

Supported By: NIMH 5 K23 MH100623; Taplin Family Foundation

Keywords: Negative Symptoms, Schizophrenia, Schizoaffective disorder, resting state functional MRI

272. Ventricles, Corpus Callosum and MIR137 in Large N Study of Schizophrenia

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Background: There is an unexplored convergence of data on lateral ventricles and corpus callosum abnormalities with impaired functioning and cognition in schizophrenia (SZ) that points to a unique opportunity to identify SZ subgroups in relation to genetics, particularly the schizophrenia GWAS risk gene mR137. We present here a recently funded NIH study (September 26, 2016), that is focused on exploring this convergence.
**Methods:** Data (1069 SZ, 1445 healthy controls) are part of the GENUS consortium (PI: Dr. Tracery Petryshen) and include sMRI, DTI, cognitive and genetic measures. Volumes will be extracted after automated masking and FreeSurfer processing. Diffusion measures will be obtained with novel methodologies: 2-tensor as well as 1-tensor tractography of DTI scans; FreeWater, a putative proxy of neuroinflammation that separates it from axonal degeneration. Genetics associations will be carried out. Clustering methods will be used to parse SZ subgroups.

**Results:** In preliminary data analyses, we had shown a significant inverse correlation between increased lateral ventricle and decreased corpus callosus volumes (del Re et al., 2015) and an inverse correlation between corpus callosus fractional anisotropy and lateral ventricle volume. Ongoing work continues to focus on extraction of lateral ventricle and corpus callosus volumetric measures; on diffusion measures of the corpus callosus; on association of volume and diffusion measures with miR137 and the genes it regulates.

**Conclusions:** The expected outcome is the identification of SZ subgroups defined by hallmark morphometric brain abnormalities in SZ patients, and by miR137 genetic pathways. This will furnish promising targets for intervention.

**Supported By:** R21-NIMH

**Keywords:** mir137, schizophrenia, sMRI, diffusion MRI

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**273. Self-Regulation of the Dopaminergic Reward System via Real Time fMRI Neurofeedback in Schizophrenia**

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**Background:** Mesolimbic dopamine dysfunction plays a crucial role in the pathophysiology of schizophrenia. However, little is known about potential disturbance in endogenous regulation of neural activity. Recently, it has been shown that healthy volunteers can actively self-regulate neural activity of the substantia nigra and ventral tegmental area (SN/VTA) using positive mental imagery. Importantly, real-time fMRI (rtfMRI) neurofeedback training improved this self-regulation ability. We applied this novel method in patients with schizophrenia (SZ) to investigate potential alterations in self-regulation of the reward system and its association with negative symptoms.

**Methods:** 14 SZ and 14 healthy controls (HC) performed a rtfMRI task with abstract visual feedback of neural activity in the SN/VTA. In the active condition, we instructed participants to voluntarily up-regulate SN/VTA activity by recalling rewarding scenes. We investigated group differences as well as correlations between neurofeedback learning and negative symptoms.

**Results:** HC but not SZ were able to actively self-regulate SN/VTA activity. After two neurofeedback training runs self-regulation was improved in HC (F=8.44, p=0.001) but not in SZ (F=0.07, p=0.93). This impaired neurofeedback learning was associated with self-reported negative symptoms.

**Conclusions:** Our results show for the first time that self-regulation of SN/VTA activity is impaired in SZ. Although neurofeedback training improves self-regulation in HC, this method might not be suitable as a potential treatment strategy in SZ in its present form. The present findings provide new insights to the to the association between negative symptoms and dopaminergic dysfunction and highlight the strengths and limitation for the use of rtfMRI neurofeedback training in schizophrenia.

**Supported By:** This work was supported by a grant of the EM D O Foundation Zurich

**Keywords:** real-time fMRI neurofeedback, Dopaminergic circuitry, Reward Learning, Schizophrenia, Negative Symptoms

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**274. MiR137 Influences White Matter Fractional Anisotropy and Cortical Surface Area in Individuals with High Genetic Risk for Psychosis**

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**Background:** The rs1625579 single nucleotide polymorphism (SNP) near the microRNA-137 (MIR137) gene has been consistently associated with schizophrenia in genome-wide analyses, and the mir-137 microRNA has been shown to regulate many other schizophrenia risk genes. The MIR137 rs1625579 risk genotype is also associated with aberrant brain structure in schizophrenia patients but not in controls. It is unknown if the observed genotype by schizophrenia diagnosis interaction may be due to epistasis between the MIR137 risk genotype and genetic risk of psychosis, or other confounds of the disorder.

**Methods:** Here, we investigated the effect of MIR137 genotype using voxel-wise analysis of white matter fractional anisotropy (FA) and more recent structural MRI-based analysis approaches including vertex-wise analysis of cortical thickness (CT), and surface area (SA). Our large sample (N=426) comprised healthy control subjects, and individuals with general high genetic risk for psychosis (first-degree relatives of patients with schizophrenia or bipolar disorder).

**Results:** Similar to what has been observed in patients with schizophrenia, we observed a significant genotype-by-group interaction in which the psychosis high-risk group with risk genotype had reduced FA, particularly in the corpus callosum. We also observed a significant genotype-by-group interaction in vertex-wise measure of SA, in which relatives with the MIR137 risk genotype had reduced surface area throughout the brain whereas the opposite effect was present in controls.

**Conclusions:** These findings provide evidence that MIR137 genotype primarily influences white matter FA in individuals with...
high familial risk of psychosis, and that the MIR137 risk genotype may be specifically associated with SA enlargement in healthy controls.

**Supported By:** This work was supported by the German Ministry for Education and Research (BMBF) grants NGFNIplus MooDS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia) and the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders) under the auspices of the e:Med program (grant numbers O1ZX1314B and O1ZX1314Q). Tristram Lett is supported by a Canadian Institute of Health Research (CIHR) Fellowship. Heike Tost acknowledges grant support by the German Federal Ministry of Education and Research (BMBF) Grant No. 01GI102. Markus M. Nöthen is a member of the Excellence Cluster ImmunoSensation, funded by the German Research Foundation (Deutsche Forschungsgemeinschaft). Franziska Degenhardt received support from the BONFOR Programme of the University of Bonn, Germany. Marcella Rietschel and Stephanie H. Witt are members of the Collaborative Research Center SFB636 of the University of Heidelberg. Andreas Meyer-Lindenberg is supported by the German Ministry of Research and Education, EU Horizon 2020, EU FP7, Innovative Medicine Initiative program and the Prix Robert de Spaelberch.

**Keywords:** Schizophrenia, psychosis phenotype, Imaging genetics, microRNA, high familial risk

### 275. Glutamate in Psychosis: In Vivo Evidence of Its Role in Treatment Response and the Potential to Modulate Glutamatergic Function

**Oliver Howes**

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**Background:** About two-thirds of patients with schizophrenia show an inadequate response to existing antipsychotic treatments, which are all D2/3 receptor blockers. Preclinical and clinical data implicates glutamatergic dysfunction in the pathoetiology of schizophrenia, but it is not known how this relates to treatment response or treatment resistance or whether it is possible to modulate glutamatergic function in patients with schizophrenia.

**Methods:** A longitudinal prospective study was conducted in drug naive first episode patients who then went onto treatment and a case-control study conducted in treatment resistant patients and matched controls (total n=120). The following clinical and imaging measures were obtained: MRS for glutamatergic indices in the anterior cingulate cortex, clinical assessment and PET imaging of dopaminergic function in a subset. A sub-set of treatment resistant patients received a challenge with a glutamate modulatory drug.

**Results:** Treatment resistant patients showed elevated glutamate levels in the anterior cingulate cortex relative to treatment responders (effect size=0.85, p<0.05). Glutamate levels showed no significant change in first episode patients during the course of early treatment (p>0.05), and there was no relationship between change in clinical measures and change in glutamate levels (all P>0.05). First episode treatment non-responders showed no alteration in dopamine synthesis capacity. Treatment resistant patients showed a blunted response to glutamate modulation.

**Conclusions:** These data indicate that treatment resistant patients show altered glutamatergic function, and show a blunted response to glutamate modulation. Antipsychotic treatment was not associated with changes in glutamatergic function. This provides evidence that glutamate dysfunction underlies the neurobiology of treatment non-response in schizophrenia.

**Supported By:** MRC

**Keywords:** Brain Imaging, First Episode Psychosis, Schizophrenia, glutamate or GABA, Antipsychotics

### 276. Hippocampal [18F]-FDOPA Uptake and Modulation of Hippocampal Activation: Implication in Schizophrenia

**Roberta Rasetti**

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**Background:** We tested for effects of dopamine function (as measured with PET) on hippocampal activity and hippocampal-parietal coupling, previously shown to be a reliable intermediate phenotype for schizophrenia, i.e. abnormal in patients with schizophrenia and their healthy siblings (Rasetti et al, 2013). Based on prior evidence of dopamine dysfunction in schizophrenia, we hypothesized that this intermediate phenotype would be modulated by dopamine tone.

**Methods:** Ninety-one healthy volunteers (ages 18-55; 57% women) had both PET and fMRI data. Presynaptic dopamine synthesis capacity was directly measured with [18F]-FDOPA PET, and the kinetic rate constant (Ki), representing specific tracer uptake, was determined. Hippocampal reactivity and coupling were measured with fMRI using a simple implicit encoding task of neutral scenes interleaved with crosshair fixation. Correlations between hippocampal [18F]-FDOPA uptake and fMRI activation, as well as hippocampal-parietal coupling, were explored. Correlations with [18F]-FDOPA uptake in dorsal striatum and ventral striatum were also tested.

**Results:** [18F]-FDOPA uptake in hippocampus was positively correlated with hippocampal and prefrontal activation (all pFWE-corrected within ROI <0.05). Moreover, hippocampal [18F]-FDOPA uptake positively correlated with hippocampus-parietal coupling (p=0.004 uncorrected, no significant results with the opposite contrast). No significant results were observed when similar analyses were conducted with [18F]-FDOPA uptake in midbrain or in ventral or dorsal striatum.

**Conclusions:** Hippocampal activation/coupling during encoding is selectively modulated by presynaptic dopamine synthesis capacity in hippocampus. These data provide direct insights into the roles of local dopamine function in hippocampus activation and may offer information to guide studies in schizophrenia.
277. Associations between Mismatch Negativity and Neurocognition and Global Functioning in Ultra-High Risk for Psychosis and First-Episode Psychosis

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Background: Mismatch negativity (MMN) is a candidate biomarker for early stages of psychosis. Although an association between MMN and functional outcome in early stages of psychosis has been shown, the effects of deviant type and cognitive deficits have not been investigated. Here, we investigated the relationships between duration MMN (dMMN) and frequency MMN (fMMN), and global functioning and cognitive function in early stages of psychosis.

Methods: Patients with first-episode psychosis (FEP), individuals with ultra-high risk (UHR), and healthy control subjects (HCs) participated in this study. We measured MMN, global functioning and cognitive function, and evaluated their relationships in each group.

Results: Correlational analyses revealed that dMMN amplitude, which was impaired in patients with FEP compared to HCs, correlated with global functioning (Global Assessment of Functioning-Functioning scale) in FEP and UHR. fMMN amplitude, which was not different between the groups, was correlated with working memory only in FEP.

Conclusions: Duration MMN may reflect a pathological process and/or abnormal development that is already present before the onset of psychosis and affects global functioning. In contrast, fMMN may reflect a pathological process present after the onset of psychosis that predicts working memory impairment. MMN may serve as a useful biomarker for the development of new treatments that improve impaired working memory and poor functional outcome in early stages of psychosis.

Supported By: NIH
Keywords: MMN, Schizophrenia, First-Episode Psychosis (FEP), Ultra-High Risk, cognitive function

278. ENIGMA-Relatives – Brain Volumes in First-Degree Relatives of Schizophrenia and Bipolar Patients

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Background: First-degree relatives of schizophrenia (SZ) or bipolar disorder (BD) patients show brain abnormalities. Through the ENIGMA-SZ and BD Working Groups, we compare different types of SZ or BD first-degree relatives (i.e., co-twins, siblings, offspring, parents) to healthy controls (HC) on global and subcortical brain measures. In this abstract, we limit ourselves to total brain (TB) and hippocampal volume.

Methods: To date, 3,033 individuals from 16 independent studies were included. MRI scans were processed with FreeSurfer. Linear mixed model analyses were performed comparing each type of relative to HC, while taking family relatedness into account. Centered age, age squared and sex
(and lithium for BD) were included as covariates. Cohen’s d effect sizes were obtained at each site and then pooled using an inverse variance-weighted random-effects meta-analysis for each relative group separately and all relatives combined. All random-effects models were fitted using the restricted maximum likelihood method.

**Results:** SZ siblings and offspring showed significantly lower TB (d = -0.19, p < 0.01 and d = -0.83, p < 0.001, respectively), as did the SZ relatives combined (d = -0.28, p < 0.001). SZ offspring had smaller hippocampal volumes than HC (d = -0.65, p = 0.001) and in all SZ relatives combined this reached trend level significance (d = -0.14, p = 0.08). No significant differences were found between BD relatives and controls.

**Conclusions:** This ENIGMA collaboration is ongoing and larger sample sizes are expected. Our preliminary findings suggest that SZ relatives, and not BD relatives, have smaller TB volume. We are currently exploring whether affected relatives explain the differences in brain volumes.

**Keywords:** Schizophrenia, Bipolar Disorder, First-degree relatives, Structural MRI, Meta-analysis

### 279. Identification of Brain Functional Connectivity Predictors of Treatment Response in Psychosis

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Icahn School of Medicine at Mount Sinai

**Background:** A substantial proportion of patients with first-time episode psychosis show a poor treatment response, which contributes to psychosocial dysfunction. This study investigates new functional neuroimaging markers to predict symptomatic outcomes in patients with first-episode psychosis.

**Methods:** We collected resting-state functional MRI (rs-fMRI) data on 72 patients with schizophrenia (n=56) or bipolar I disorder (n=16) (mean age = 26.5, 16 females) presenting their first psychosis onset within 5 years. For each individual, the brief psychiatric rating scale (BPRS) was collected at the time of the scan and 234 days (sd: 184 days) later. Rs-fMRI data were preprocessed in SPM12. They were then parcellated based on an anatomical 638-region atlas. Functional connectivity matrices were computed for each individual. The relation between treatment response and the functional connectivity was investigated using the network-based statistics toolbox (t>3.5; 5,000 permutations). The total BPRS at time 1, the time between洗 treatment response and the functional connectivity was assessed, and in all SZ relatives combined this reached trend level significance (d = -0.14, p = 0.08). No significant differences were found between BD relatives and controls.

**Results:** Improvement at Time 2 (evaluated by the total BPRS) was mostly associated with increased connectivity between primary and associative cortices (sensorimotor cortex and middle frontal gyrus; visual cortex and superior temporal gyrus) at Time 1. In contrast, improved (reduced) positive symptoms at time 2 was related to reduced connectivity involving the ventral anterior cingulate and middle temporal gyr at Time 1.

**Conclusions:** Our results show evidence that rs-fMRI measures can predict clinical status of patients with psychosis. Early identification of patients that may fail to achieve remission could assist in the development of stratified treatment plans.

**Supported By:** R01MH104284-01A1

**Keywords:** resting-state, Prediction of Treatment Outcome, Early psychosis

### 280. Rural and Urban Childhood Environment Effects on Episodic Memory

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**Background:** Childhoods in urban or rural environments may differentially affect risk for neuropsychiatric disorders. Here, we leveraged on dramatic urbanization and rural-urban migration since the 1980s in China to explore the hypothesis that rural or urban childhoods may differentially influence memory processing and neural responses to neutral and aversive stimuli.

**Methods:** We examined 420 adult subjects with similar current socioeconomic status and living in Beijing, China, but with differing rural (n = 227) or urban (n = 193) childhoods. In an episodic memory paradigm scanned in a 3T GE MRI, subjects viewed blocks of neutral or aversive pictures in the encoding and retrieval sessions.

**Results:** Episodic memory accuracy for neutral stimuli was less than for aversive stimuli (p < 0.001). However, subjects with rural childhoods apparently performed less accurately for memory of aversive but not neutral stimuli (p < 0.001). In subjects with rural childhoods, there was relatively increased engagement of bilateral striatum at encoding, increased engagement of bilateral hippocampus at retrieval of neutral and aversive stimuli, and increased engagement of amygdala at aversive retrieval (p < 0.05 FDR corrected, cluster size > 50).

**Conclusions:** Rural or urban childhoods appear associated with physiological and behavioral differences, particularly in the neural processing of aversive episodic memory at medial temporal and striatal brain regions. It remains to be explored the extent to which these effects relate to individual risk for neuropsychiatric or stress-related disorders.

**Supported By:** NIH R01MH101053; NSFC 81361120395

**Keywords:** childhood, environmental factors, Episodic Memory, Hippocampus, striatum

### 281. Intracortical Myelination within the Frontal Lobe as a Potential Biomarker for Therapeutic Effectiveness in Antipsychotics Using MRI with Selective Myelin-Lipid Suppression at 1.5T and 3T

**Todd Tishler**², George Bartzokis², Larry Alphs¹, Brianne Brown¹, Yong Yue¹, JP Villablanca², Kenneth Subotnik², Keith Nuechterlein², and Benjamin Ellingson³

**Background:** Childhoods in urban or rural environments may differentially affect risk for neuropsychiatric disorders. Here, we leveraged on dramatic urbanization and rural-urban migration since the 1980s in China to explore the hypothesis that rural or urban childhoods may differentially influence memory processing and neural responses to neutral and aversive stimuli.

**Methods:** We examined 420 adult subjects with similar current socioeconomic status and living in Beijing, China, but with differing rural (n = 227) or urban (n = 193) childhoods. In an episodic memory paradigm scanned in a 3T GE MRI, subjects viewed blocks of neutral or aversive pictures in the encoding and retrieval sessions.

**Results:** Episodic memory accuracy for neutral stimuli was less than for aversive stimuli (p < 0.001). However, subjects with rural childhoods apparently performed less accurately for memory of aversive but not neutral stimuli (p < 0.001). In subjects with rural childhoods, there was relatively increased engagement of bilateral striatum at encoding, increased engagement of bilateral hippocampus at retrieval of neutral and aversive stimuli, and increased engagement of amygdala at aversive retrieval (p < 0.05 FDR corrected, cluster size > 50).

**Conclusions:** Rural or urban childhoods appear associated with physiological and behavioral differences, particularly in the neural processing of aversive episodic memory at medial temporal and striatal brain regions. It remains to be explored the extent to which these effects relate to individual risk for neuropsychiatric or stress-related disorders.

**Supported By:** NIH R01MH101053; NSFC 81361120395

**Keywords:** childhood, environmental factors, Episodic Memory, Hippocampus, striatum

**Supported By:** NIH R01MH101053; NSFC 81361120395
Results: At 1.5T, ICM of schizophrenia patients was higher obtained and segmented, and ICM was quantified with antipsychotics (NCT02431702). Coronal oblique proton patients comparing paliperidone palmitate with oral antipsychotic therapy. Consistent with findings at 1.5T, ICM of schizophrenia patients at 3T was higher as a function of duration of antipsychotic exposure over the first year of treatment but declined thereafter. 2) Modications of inversion times and other parameters allowed for close correlation between 1.5T and 3T readings. 3) Consistent with findings at 1.5T, ICM of schizophrenia patients at 3T was higher as a function of duration of antipsychotic exposure over the first year of treatment (r=.68, p<.03).

Conclusions: Inverted U-shaped function of ICM with duration of oral antipsychotic exposure is consistent with initial clinical response followed by increasing nonadherence and worsening symptoms. Preliminary results at 3T demonstrate feasibility of multicenter measurements and indicate similar initial increases in ICM as a function of antipsychotic exposure. ICM measurements show promise as a potential biomarker for evaluation of therapeutic effectiveness.

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Keywords: Schizophrenia, Intracortical myelination, Antipsychotics, MRI, Biomarkers


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Background: Evidence suggests that the prefrontal cortex is involved in executive control and executive dysfunction is implicated in schizophrenia. Reduced dopamine D2/D3 receptor binding potential (BP) has been reported in schizophrenia, and the correlations with neuropsychological test scores have been positive and negative for different tasks. The study aim was to examine the relation between dopamine D2/D3 receptor levels with frontal and temporal neurocognitive performance in schizophrenia.

Methods: Resting-state 18F-fallypride PET was performed on 20 medication-naïve plus 5 previously-medicated patients with schizophrenia and 19 normal controls. Striatal and extrastriatal dopamine D2/D3 receptor levels were quantified as BP using fallypride imaging. Magnetic resonance images in standard Talairach position were co-registered to the fallypride images, and the AFNI stereotactic atlas was applied. Two fronto-temporal related tasks were chosen: Wisconsin Card Sorting Test and California Verbal Learning Test.

Results: We found a positive correlation between BP and WCST and CVLT performance in controls, while a negative correlation was found in schizophrenia. Patients with schizophrenia...
showed negative correlations between performance and BP. In line with model-based systems theory, we found a significantly more positive correlation between BP and short-delay performance (model-free) in the ventral striatum in controls than the correlation between BP and WCST categories (model-based).

**Conclusions:** Our findings reinforce the concept of distributed influence of dopamine on performance involving striatal/extrastriatal regions. These influences are trait-like extending across cognitive tasks in healthy subjects. Our findings are consistent with the widely interconnected-network patterns observed in fMRI connectivity studies rather than with a restricted network of localized, and specialized neural loci.

**Supported By:** Major funding was provided by the Kettering Health Network Foundation. Dr. NS Vyas is supported by the Winston Churchill Travel Fellowship 2016-17 by the Winston Churchill Memorial Trust.

**Keywords:** Schizophrenia, Positron Emission Tomography, Dopamine, Prefrontal Cortex, cognition

**284. Risk Taking Behavior is Associated with Anterior Cingulate Volume in Marijuana Using Adolescents**

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**Background:** Marijuana (MJ) is one of the most commonly used illicit drugs among adolescents in the US. Numerous studies have highlighted structural and functional brain alterations that are associated with MJ use, including prefrontal changes. One of the behaviors linked to both substance use and the anterior cingulate (ACC) is risk-taking. Therefore, we hypothesized that adolescent MJ users would exhibit increased risk-taking behavior, which would be associated with anterior cingulate morphometry.

**Methods:** 71 MJ-using and 62 healthy control adolescents completed a structured clinical interview (SCID) to assess MJ use and the Balloon Analogue Risk Task (BART) to assess risk-taking behavior. Structural magnetic resonance imaging (MRI) data were acquired on a 3T Trio and analyzed using FreeSurfer software to acquire regional brain volumes.

**Results:** On the BART, MJ-using adolescents showed significantly increased number of pumps ($p=0.01$), increased number of explosions ($p=0.04$) and greater amount of money earned ($p=0.009$). Right ACC volume was significantly correlated with the amount of money earned in the MJ group ($p=0.04$) but not in controls. No significant between-group differences were observed for ACC volume.

**Conclusions:** MJ-using adolescents exhibited greater risk-taking behavior, which was correlated with ACC morphometry in MJ users. Previous studies have implicated the ACC in impulsive and risk-taking behavior. Our results highlight the importance of further evaluating the association between ACC and risky behavior in MJ-using adolescents to understand whether this association is related to risk for onset of drug use and/or neurotoxic effects of MJ use.

**Supported By:** RO1-DA020269

**Keywords:** Marijuana, Anterior cingulate, Adolescents, Neuroimaging, Risk-Taking

**285. The Association of Anger and Hippocampal Volumes in Marijuana-Using Adolescents**

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**Background:** Previous research suggests a relationship between marijuana (MJ) use, neurocognitive deficits and clinical behavior. For example, cognitive control, impulsivity and anger are evident in MJ smokers. Moreover, the hippocampus has been shown to play a role in anger and aggression. Nevertheless, the association between anger and aggression and the hippocampus in adolescent MJ users is not clear. This study explored the relationship between hippocampal volumes and measures of anger in adolescent MJ users and HC.

**Methods:** 33 MJ using adolescents and 28 non-using adolescents (49 male and 12 female) were included in this study. Participants completed a clinical interview, behavioral measures and magnetic resonance imaging (MRI) on a 3T Trio scanner. Structural MRI was obtained and analyzed using FreeSurfer software to acquire regional brain volumes. The Buss-Perry Aggression Questionnaire (BPAQ) subscales were completed to measure anger and aggression and MJ use was determined by a semi-structured self-report measure.

**Results:** Positive correlations were found between the left ($r=0.486, p=0.007$), and total ($r=0.521, p=0.004$) hippocampal volumes and the Anger subscale in the BPAQ aggression questionnaire in the MJ group. There were no significant associations between hippocampal volumes and anger in the HC group. Additionally, no significant differences were observed between the MJ and HC groups.

**Conclusions:** Results show that hippocampal volume is associated with anger in MJ using adolescents. Previous studies have shown hippocampal volumes are associated with aggression in sexual trauma. Current study findings suggest that hippocampal volume may be a critical region in understanding the underlying anger in MJ using adolescents.

**Supported By:** 1R01 DA020269-01

**Keywords:** Marijuana, Adolescents, Neuroimaging, Anger, Hippocampal Volume

**286. Dopamine Transporter and Reward Anticipation in Psychiatric Patients: A Positron Emission Tomography and Functional Magnetic Resonance Imaging Study**

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Biological Psychiatry May 15, 2017; 81:S1–S139 www.sobp.org/journal S117
**Background:** Dopamine function and reward processing are highly interrelated and involve common brain areas that mainly belong to the mesocorticolimbic pathways. Impairments of both systems have been involved in numerous psychiatric disorders. However, whether alterations in the dopamine system underlie altered reward processing across psychopathologies remains unknown.

**Methods:** We sought to explore the relationship between dopamine function and reward anticipation in healthy volunteers and psychiatric patients with schizophrenia, depression, and addiction. We performed Positron Emission Tomography (PET) with [11C]PE2I to assess the dopamine transporter (DAT) availability as a marker of presynaptic dopamine function, and functional MRI (fMRI) using a modified Monetary Incentive Delay task to assess reward-related neural activity. Voxel-based multimodal imaging analysis was performed with SPM software.

**Results:** Twenty-seven participants were included in the study. Across all participants we found a significant relationship between DAT availability and reward-related activations within the mesolimbic pathway.

**Conclusions:** We evidenced a direct link between a marker of the dopamine system and reward anticipation, which transcend diagnostic categories in psychiatric patients. The findings underlie the interest of a dimensional approach in psychiatry and the common use of PET and fMRI to assess dopamine and reward neural networks from molecular to functional level.

**Supported By:** INSERM, ANR, PHRC, MILDECA, MILDT

**Keywords:** Dopamine transporter, Reward, Multimodal neuroimaging, Dimensional

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**287. Neuroadaptations to Chronic Ketamine Exposure: A Parallel Human and Mouse MRI Imaging Study**

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**Background:** Recreational ketamine use is associated with negative effects on cognition and psychological well-being, as well as changes in frontal lobe brain structure. These data may however be confounded by abuse of other psychotropic drugs and environmental or genetic susceptibility factors. To clarify this, we compared magnetic resonance imaging (MRI) derived volumetric data from human ketamine users and poly-drug controls with MRI data from mice exposed to intermittent or daily repeat ketamine administration.

**Methods:** Volumetric MRI data acquired from ketamine users (n=14) and poly-drug controls (n=13) were analysed using freely available tools in Freesurfer and FSL. MR images acquired from male C57Bl6/J mice (aged 10-11 weeks; n=15 per group), repeatedly administered ketamine (20 mg/kg) either daily for 14 days, or intermittently every 3 days for 30 days, with saline as a control, were analysed using tensor-based morphometry (Richetto et al, 2016).

**Results:** Human ketamine users displayed significant clusters of decreased grey matter volume across the cortex, including the right paracentral lobule (3.47±0.5 cm\(^3\) vs 4.36±0.64 cm\(^3\), F= 17.31, p=0.00035). Both daily and intermittent ketamine administered mice displayed clusters of volumetric change across the brain including, within intermittent mice, a significantly larger left frontal lobe (28.19±0.67 cm\(^3\) v 27.34±0.65 cm\(^3\), F= 11.72, p=0.021) and left entorhinal cortex (6.63±0.24 cm\(^3\) v 6.25±0.34 cm\(^3\), F= 14.36, p=0.021).

**Conclusions:** Repeated ketamine exposure has differential effects on MRI measures of brain volume in humans and mice. These data are consistent with the likelihood of confounds in the human data, such as additional psychotropic drug use.

**Supported By:** King’s Health Partners; Guy’s and St. Thomas’ Charitable Trust; National Institute for Health Research (Maudsley Biomedical Research Centre); Medical Research Council.

**Keywords:** Ketamine, MRI, Addiction, Neuroimaging, Translational research

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**288. Δ-9-THC Modulates Fear Processing and Functional Connectivity in an Emotional Salience Task**

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**Background:** Delta-9-tetrahydrocannabinol (Δ-9-THC) the primary psychoactive constituent of cannabis is established to have acute psychotomimetic and anxiogenic effects. How Δ-9-THC impacts on the critical substrate for emotional salience and functional connectivity of the fear circuit remains to be fully explored.

**Methods:** We report on 35 healthy male controls in Δ-9-THC challenge in a placebo-controlled events-based fMRI study. Subjects were administered oral Δ-9-THC 10mg or placebo on different sessions around two hours prior to an emotional salience task during scanning. Individuals were exposed to 60 facial stimuli of neutral facial expression, 50% fear or 100% fear. The main outcome measure was fMRI BOLD activation. Whole Brain analysis and functional connectivity analysis was undertaken.

**Results:** Compared to placebo, Δ-9-THC significantly modulated activity in the right amygdala and right superior temporal gyrus with decreased activation at 100% fear. At the right superior temporal gyrus, right parahippocampal gyrus and midbrain there was significantly increased BOLD activation compared to placebo at 50% fear. Using the right amygdala as a seed cluster revealed functional connectivity with increasing fear with left temporal and limbic structures. On Drug by Valence analysis Δ-9-THC challenge was associated with modulation of connectivity of the right amygdala with a region involving the left anterior cerebellum and brainstem.
Conclusions: In the largest series to date we demonstrate modulation of regional brain activity and connectivity in response to fear after Δ-9-THC. Cannabis use may increase inappropriate activation to intermediate fear whilst failing to activate regions when high fear is needed.

Supported By: Medical Research Council, United Kingdom and Psychiatry Research Trust, United Kingdom.

Keywords: Cannabis, Fear, emotional face processing, Functional MRI, Functional connectivity

289. High Fructose Consumption Promotes Alterations in Affective-Like Behaviors and Increased Activity of Complement Pathways in the Hippocampus

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Background: Fructose consumption has increased by over 25% since the 1970s, and adolescents consume the greatest quantity of fructose. Fructose is associated with metabolic dysfunction and peripheral inflammation, and previous work from our group demonstrated that a high-fructose diet in male rats during adolescence increases adiposity, elevates plasma corticosterone, and increases depressive- and anxiety-like behavior. The current study addressed the hypothesis that consumption of a high-fructose diet promotes activity of the complement pathway and alters synaptic integrity.

Methods: Male rats consumed a high-fructose diet for 10 weeks initiated at weaning. In adulthood, expression of C4b, Cfb, and C1q in the hypothalamus and hippocampus were assessed by qRT-PCR. Protein concentrations of complement proteins, synaptophysin, and PSD95 in the hippocampus were assessed by immunoblotting.

Results: Consumption of a high-fructose diet throughout adolescence caused increased expression of Cfb and C4b in both the hypothalamus (C4b: t11=14.62; p<0.0001 Cfb: t11=7.793; p<0.0001) and the hippocampus (C4b: t11=4.442; p=0.0010; Cfb: t11=2.352; p=0.0384). Although neither synaptophysin nor PSD95 differed in normalized density between chow- and fructose-fed rats (p > 0.05), complement expression predicted synaptic markers in a linear regression model. Specifically, lower Cfb expression predicted synaptic density such that lower Cfb expression indicated higher synaptophysin density (B=1.1143, t8=3.047, p=0.0159).

Conclusions: These data demonstrate that high-fructose diet consumption during adolescence promotes increased expression of complement in the hypothalamus and hippocampus, and suggest that complement expression may predict synaptic markers. Future studies will determine the extent to which complement mediates alterations in synaptic integrity and behavior following developmental exposure to a high-fructose diet.

Keywords: Adolescent Depression, diet, synaptic plasticity, Neuroinflammation, Inflammation

290. Altered Behavior, Sleep, and Epileptiform Activity in a Perinatal Multiple Hit Immune Activation Mouse Model of Autism Spectrum Disorder (ASD)

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Background: Accumulating evidence supports a role for immune system function in autism spectrum disorder (ASD). Previous research shows that immune activation during critical developmental periods can trigger a phenotype that reproduces core features of ASD, including altered social interaction and communication. We recently developed a “multiple hit” immune model, whereby mice are exposed to repeated perinatal immune activation and then evaluated in tests representing behavioral domains dysregulated in ASD.

Methods: Pregnant mice (C57/BL6) were injected with Poly:ηC (20 mg/kg) on embryonic day 12.5 (E12.5) and a subset received a second hit of lipopolysaccharide (LPS; 10mg/kg) on postnatal day 9 (PND9). We then examined numerous behaviors related to key features of ASD over a period of weeks. We also used a wireless electroencephalography (EEG)/electromyography (EMG) system to assess two physiological measures commonly dysregulated in ASD: sleep and epileptiform activity.

Results: Our multi-hit model produced a behavioral phenotype that resembles ASD in numerous domains, with significant alterations (p<0.05) in pup ultrasonic vocalizations (USVs), adult USVs, social interaction, and open field behavior. Interestingly, males were more prominently affected than females. Postnatal LPS treatment was sufficient to produce many of these effects. In the EEG telemetry study, the multi-hit treatment produced significant alterations (p<0.05) in activity, temperature, and sleep (increased slow-wave sleep). Further, postnatal LPS produced elevations in epileptiform activity (spike-wave discharges).

Conclusions: Perinatal immune activation produces a sex-dependent behavioral phenotype, accompanied by alterations in sleep and epileptiform activity. This models key features of ASD, supporting an immunological involvement in subtypes of this condition.

Supported By: Robert and Donna Landreth Fund, The Nancy Lurie Marks Family Foundation, and The Teamsters Local 25 Autism Fund

Keywords: Autism Spectrum Disorder, Immune Activation, Behavior, Sleep, epilepsy

291. Relationship between Sub-chronic C-Reactive Protein Exposure and Risk for Post Traumatic Stress Disorder

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Background: The pro-inflammatory marker C-reactive protein (CRP) has been associated with post traumatic stress disorder (PTSD). We tested the hypothesis that sub-chronic CRP exposure modulates behavioral and inflammatory responses using a predator stress PTSD model.

Methods: Cohorts of 5-7 male C57Bl/6J mice received intraperitoneal injections once daily for four days with either 1 mg/kg human CRP (hCRP) or vehicle. Six hours after the fourth injection, mice were exposed to predator stress (10 min roomed with a laboratory cat), or handled (stress control). After two weeks, mice were tested for trauma memory by measuring exploration of a cue scented with dirty cat litter. Mice were then sacrificed the next day to quantify plasma inflammatory markers.

Results: Six hours after administration, hCRP was detected in mouse plasma (9,220 ng/mL), indicating this dose conferred significant hCRP exposure. Stressed vehicle-treated mice exhibited significantly increased “trauma” cue avoidance compared to handled controls (p = 0.034), indicating reliably induced anxiety-like behavior. Surprisingly, hCRP-treated mice trended towards less trauma cue avoidance (p = 0.070). Plasma mouse CRP was reduced in the stressed group treated with hCRP compared to the stressed vehicle group (p = 0.017).

Conclusions: This preliminary study indicates sub-chronic hCRP exposure does not increase risk for PTSD-like behavior and may have been protective. Four day bolus injections however may not adequately model chronic inflammation, but instead may support immune suppression. Further studies with long-term hCRP exposure are needed to determine if hCRP induces PTSD risk.

Supported By: R25 MH101072
Keywords: PTSD - Posttraumatic Stress Disorder, Mouse, C-reactive protein, Inflammation

292. Elevations and Increased Variability of Blood-Based Pro-Inflammatory Markers among Patients with Bipolar Disorder

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Background: The role of inflammation in bipolar disorder (BD) is increasingly recognized; most studies have not examined dynamics of innate immunity. We compared mean levels and intra-individual variability (IIV) of blood-based inflammatory markers between those with and without BD and examined biopsychological correlates.

Methods: We analyzed baseline data of 17 BD patients and 40 healthy comparison (HC) participants from an ongoing longitudinal study. At three visits over two weeks, blood was drawn and height, weight, and blood pressure (BP) were measured; baseline symptoms were assessed once. Mean and IIV across the three visits of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-a), and interleukin-6 (IL-6) were compared between groups. Relationships to biopsychological variables were examined.

Results: Groups were comparable on age, gender, ethnicity, body mass index, and proportion of smokers; BD had higher Framingham stroke risk. Mean CRP, TNF-a, and IL-6 was higher in BD than HC. Levels of CRP were more variable across three visits in BD than HC even after controlling for mean differences. Patients with more depressive symptoms had higher mean CRP and IL-6 levels; mania symptom severity was also related to higher mean IL-6. BD patients with higher baseline systolic BP had higher IV of CRP and IL-6.

Conclusions: Elevations of three pro-inflammatory markers were observed in BD, and for CRP, there was greater instability across two weeks. Mean levels were mood-related; variability seemed more linked to cardiovascular dysfunction. Future analyses will relate repeated cognitive assessments and daily mood ratings to inflammatory markers.

Supported By: NIMH R01 MH103318
Keywords: Inflammation, Bipolar Disorder, IL-6, TNF, C-reactive protein

293. The “Cytokine Fingerprint” of Perinatal Depression and Anxiety

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Background: Prior studies of perinatal psychiatric illness and the immune system have largely focused cross-sectionally on correlations between depression and individual inflammatory markers.

Methods: The Viral Immunity in Pregnancy Study measured mood (Beck Depression Inventory, BDAI) and anxiety (State-Trait Anxiety Inventory, STATE) along with 24 different cytokines at 5 points in pregnancy and postpartum in 48 women. Cytokine trajectory over time by depression/anxiety status was modeled using linear mixed effects models with random intercept and slope. Cluster analysis divided subjects into 2 groups based on their third trimester cytokine values.

Results: IL-6 (p =.001), GCSF (p =.004), and MIP1α (p <.001) were significantly different across time by categorical BDAI score, with more depressed subjects having higher levels. IL-6 (p =.019) was significantly different across time by categorical STATE score, and more anxious subjects had higher levels of MIP1α, GMCSF, IL-8, and IL-6 at individual time points (p =.016, .038, .008, and <.001, respectively). In cluster analysis, Group 1, with higher STATE score (median 29 vs. 26) and higher cytokine values, had lower proportions of African-American subjects (25% vs. 58.6%), overweight and obese (36.4% vs. 65.4%), pregnancy complications (8.3% vs 20.7%), preterm births (0 vs. 10%), and those married or living with a partner (58.3% vs. 72.4%); these differences did not reach statistical significance in our small sample.

Conclusions: Our results extend previous findings by examining patterns of cytokine change across time and using cluster analysis to show differences among groups by cytokine and anxiety level.

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294. Positive Association between Toxoplasma Gondii IgG Serointensity and Depression in the Old Order Amish

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Background: Toxoplasma gondii (T.gondii) IgG positivity and serointensity, and markers of low-grade inflammation, have been previously associated with suicidal self-directed violence (SSDV). Although associations with unipolar depression have also been investigated, results have been inconsistent, possibly as a consequence of high heterogeneity of clinical samples. Thus, we now studied in a more homogeneous population, (i.e. Amish) reactivation may improve therapeutic control in T.gondii seropositive patients with depression and/or SSDV.

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Keywords: Depression, Toxoplasma gondii, Old Order Amish, Hopelessness, Anhedonia

295. Elucidating Adaptive Roles of Microglia in Chronically Stressed Mice

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National Institute of Mental Health

Background: Psychosocial stressors induce central and peripheral immune pathway signaling that is increasingly thought to be relevant to the pathophysiology of depression. We hypothesized that chronic social defeat stress (CSD) in rodents can precipitate an immune reaction in the brain directly through activation of resident microglia and that the degree and kind of activation are dependent on the psychological status of the animal following the stress.

Methods: Mice exposed to CSD become subordinate, and mice susceptible to CSD (CSD-S) show enduring deleterious psychological and physiological consequences. However, a subset avoids this outcome, which we call resilient (CSD-R). We first performed a microarray analysis on microglia isolated from CSD-S and CSD-R mice to understand how these cells differentially respond to and perhaps contribute to stress adaptability. Next, a series of ex-vivo and in-vivo experiments was performed to test the array results.

Methods: In 306 Old Order Amish, age range 18-87(median 44), with 191 (62.4%) women, all participants in the Amish Wellness Program in Lancaster,PA , we had obtained both T.gondii IgG-titers and neopterin levels (by ELISA), and depression screening questionnaires (current and life-long PHQ9 N=280 and PHQ2 N=26). Current and life-long anhedonia, dysphoria-hopelessness, and combined depression phenotypes were analyzed in relationship to logtransformed-titers, seropositivity, and logtransformed-neopterin with linear models with adjustment for age and sex.

Results: Serointensity was significantly associated with current dysphoria-hopelessness (p<0.045) and combined anhedonia and dysphoria-hopelessness (0.040), while associations with simple anhedonia scores, life-long depression phenotypes, were not significant. There was also a marginal trend for associations between seropositivity and current dysphoria-hopelessness (p<0.057) and their combination (p<0.055). Logneopterin- associations with any depression phenotype were not significant.

Conclusions: These results should lead to larger longitudinal studies that could test if hopelessness-dysphoria is associated IgG-titers elevations, possibly secondary to T.gondii reactivation, and to interventional studies to test if reducing T.gondii reactivation may improve therapeutic control in T.gondii seropositive patients with depression and/or SSDV.
stressed mice. However, CSD does not cause extravasation of peripheral monocytes into brain.

**Conclusions:** CSD-S microglia are more phagocytic and secrete molecules that break down the BBB. These kinds of activities represent a CNS-centric inflammatory state that may contribute to the susceptible phenotype.

**Supported By:** NIH IRP

**Keywords:** Microglia, psychoneuroimmunology, Blood brain barrier, social defeat stress, macrophage

296. Correlating Peripheral and Central Markers of Neuroinflammation to PET Imaging of Translocator Protein (TSPO)

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1NIMH, 2Janssen Research & Development, LLC

**Background:** Neuroinflammation is a predisposing factor for major depressive disorder (MDD). We recently showed differences in translocator protein 18 kDa (TSPO), an indirect marker of neuroinflammation, in patients with MDD. Specifically, TSPO binding was increased in unmedicated but not medicated MDD subjects compared to healthy controls (HCs). The aim of this study is to determine if central and peripheral inflammatory biomarkers correlate with these TSPO differences.

**Methods:** Unmedicated (n = 12), medicated MDD (n = 16) and HC (n = 20) subjects who previously underwent PET imaging were included. We obtained peripheral blood samples on all subjects and cerebral spinal fluid (CSF) collection was elective. We utilized Enzyme-Linked Immunosorbent Assay (ELISA) to measure peripheral levels of various pro- and anti-inflammatory proteins.

**Results:** Interim results show that in plasma, TNF-alpha and quinolinic acid levels are significantly elevated in medicated MDD subjects compared to unmedicated subjects and HCs. In CSF, vascular endothelial growth factor levels are increased in medicated MDD subjects compared to HCs and interferon-gamma levels are higher in unmedicated MDD subjects compared to HCs. All differences are significant at a p<0.05 level. There was no correlation of plasma or CSF inflammatory markers to TSPO binding.

**Conclusions:** These preliminary results indicate significant differences in peripheral and central markers of inflammation depending on mood state and treatment status but how this relates to TSPO binding, and neuroinflammation, must be better characterized. These findings are important to help with understanding the heterogeneity of MDD and for development of novel therapeutic agents.

**Supported By:** IRP-NIMH-NIH-DHHS; Janssen Pharmaceuticals, Inc.

**Keywords:** Inflammation, Neuroinflammation, Translocator Protein (TSPO), Kynurenic acid, VEGF

297. Neopterin and Zinc Differentially Predict Mood Severity in Men and Women with Bipolar Disorder

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**Background:** Symptomatic mood states in bipolar disorder (BD) may be associated with elevated inflammatory markers, however this may differ in men and women. The aim of the current work was to examine the association of zinc, a neural modulator, and neopterin, an inflammatory marker, with mood severity in BD men and women.

**Methods:** Subjects with DSM IV bipolar disorder I and II (BD, N=27) were recruited through the Pennsylvania Psychiatric Institute (PPI) during an acute mood episode. Participants were fasting for at least 6 hours when blood was drawn for biomarkers. The second serum sample was collected when the subject was asymptomatic, or after 3 months had elapsed.

**Results:** Serum zinc concentration was significantly lower in the BD group than in the healthy control (HC) group at baseline (p=0.04). Plasma neopterin concentrations at baseline were not different between HC and BD participants, on average. We found a significant interaction between gender and neopterin concentrations associated with mania at baseline (p=0.013). We also found a significant interaction of gender and serum zinc associated with depression severity at baseline (p=0.03). Follow-up analysis revealed a significant increase in serum zinc between baseline and follow up (p=0.02).

**Conclusions:** We report that severity of mania may be associated with neopterin in men, while depression severity may be associated with zinc in women. Our report also highlights the importance of analyzing gender in human studies of BD and the potential for differences in the underlying pathophysiology between men and women.

**Supported By:** NIH KL2

**Keywords:** Mood disorders, Bipolar Disorder, Inflammation, Inflammatory Markers, Biomarkers

298. Peripheral inflammation, Physical Activity and Cognition in Bipolar Disorder

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**Background:** Alterations in peripheral inflammation, physical activity (PA), and cognition have been reported in bipolar disorder (BD), yet little is known about the relationships between these factors. We examined associations among pro-inflammatory cytokines, objectively measured PA, and executive functioning...
resulting in the clinical outcome of anhedonia. Here, we sought (GABA) dysfunction in adolescent major depressive disorder (MDD).

Methods: Twenty-two BD and 43 HC participants’ data were analyzed from an ongoing longitudinal study. All participants were administered cognitive tests and health questionnaires, and wore an actigraphy watch measuring degree of movement for two weeks. Blood samples were obtained from a subsample of participants (15 BD and 23 HC) and were assayed for interleukin-6 (IL-6) and C-reactive protein (CRP). PS and EF composite scores were derived from averaging z-scores of relevant tasks.

Results: Groups were comparable on age, gender, ethnicity, body mass index (BMI) and stroke risk. The BD group had significantly higher levels of IL-6 and exhibited worse EF and PS performance than the HC group. While there were no group differences in PA or CRP, higher average PA across the two-week period was associated with lower CRP in the BD group only. This relationship remained significant after accounting for stroke risk and BMI.

Conclusions: This preliminary investigation suggests that pro-inflammatory cytokines linked to vascular risk, particularly CRP, may be sensitive to levels of PA. Further, BD patients may be particularly responsive to the beneficial effects of PA on inflammation. Future studies will examine the impact of mood on PA.

Supported By: NIMH R01 MH103318

Keywords: Bipolar Disorder, Inflammation, physical activity, cognition

299. Inflammation, γ-Aminobutyric Acid Deficits, and Anhedonia in Depressed Youth
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Background: Inflammatory processes and γ-aminobutyric acid (GABA) deficits have both been separately implicated in reward dysfunction in adolescent major depressive disorder (MDD), resulting in the clinical outcome of anhedonia. Here, we sought to examine the interrelations between inflammation, GABA levels, and anhedonia in depressed youth.

Methods: Forty-four psychotropic medication-free youth with MDD and 36 healthy controls (HC; 12–21 years old) underwent a proton magnetic resonance spectroscopy scan; plasma levels of 13 cytokines were measured in a subset of this sample (MDD = 33, HC = 26). Anhedonia was evaluated both dimensionally and categorically.

Results: GABA levels were reduced in depressed youth compared to HC [F(1, 77) = 8.08, p = .006]. When patients were classified based on the presence of anhedonia, only the anhedonic MDD subgroup had lower GABA levels compared to HC [p = .002]. Dimensional analyses further showed that GABA levels correlated with anhedonia severity in MDD [r = −.33, p = .03]. Additionally, both interleukin 7 (IL7) [p = −.36, p = .04] and IL6 [p = −.35, p = .04] correlated with GABA levels in MDD, and IL4 [p = .38, p = .03] was related to anhedonia severity. However, Sobel’s test of mediation did not show that alterations in GABA mediated the relationship between inflammation (IL4) and anhedonia in MDD [CI: −.04, .05].

Conclusions: While both inflammation and alterations in GABA are independently related to anhedonia severity, the complete mechanism underlying these complex relationships is still unclear in adolescent MDD and warrants further investigation.

Supported By: NIH R01MH101479; NIH R01MH095807

Keywords: Inflammation, GABA, Adolescence, Anhedonia, brain reward circuit

300. Improvement in Measures of Depressed Mood and Anhedonia in Two Randomized, Placebo-Controlled Phase III Studies of Sirukumab, a Human Anti-Interleukin-6 Antibody, in Patients with Rheumatoid Arthritis
Yu Sun, Gayle Wittenberg, Guang Chen, Wayne Drevets, Benjamin Hsu, and Mark Curran

Janssen Research & Development, LLC

Background: Interleukin-6(IL-6) is involved in neuronal plasticity, stress coping and depression. Depressive symptoms are prevalent in patients with rheumatoid arthritis (RA), a disease with high peripheral IL-6. Previous analysis of a phase II study showed that anti-IL-6 treatment can alleviate depressive symptoms in RA patients.

Methods: Here we analyzed 2 Phase III, double-blind, placebo-controlled trials of sirukumab, an anti-IL-6 monoclonal antibody, in patients with active RA and serum CRP $\geq 8$mg/L or ESR $\geq 28$mm/h despite disease-modifying anti-rheumatic drugs (DMARDs) or anti-TNF therapy. Patients were grouped by presence/absence of prevalent depressed mood and anhedonia (PDMA), based on two core depressive symptoms in the SF-36, requiring one rated as present at least ‘most of the time’ and the other ‘some of the time’. Efficacy on depressive symptoms was evaluated directly and with adjustment for RA severity using the DAS28-CR. RA response was defined by achieving ACR50.

Results: At baseline, 19%-22% of patients were classified as PDMA. Sirukumab treatment, compared to placebo, significantly improved depressive symptoms by week 8 among PDMA patients in both studies (p=0.0216, p=0.0458). The within-treated-group mood effects remained significant after co-varying for changes in RA severity (p<0.0001) and in patients designated as RA non-responders (p<0.0001) while between-group effects reduced to trends. Meta-analysis of 4 anti-IL-6 studies (1 siltuximab and 3 sirukumab) revealed that anti-IL-6 treatment may help alleviate depressive symptoms (Standardized Mean Difference = 0.25, p=0.03).

Conclusions: Consistent with previous result, our findings showed that peripheral anti-IL-6 treatment is associated with improvement in depressive symptoms in RA patients, supporting a role for IL-6 dysfunction in depression.

Supported By: Internal Grant from Janssen Research & Development LLC

Keywords: Major Depressive Disorder (MDD), IL-6, Neuroimmunology
301. Whole Blood Gene Expression Profiling to Identify Dimensions of Immune Function in Depression

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Background: Inflammation is an important driver of depression. Previous work has treated depression as a unified construct when examining immune markers; however not all depressed patients have inflammation. This project is designed to extend prior work by examining variation in basal immunity in depression.

Methods: 40 adults in a SCID-validated current depressive episode were phenotyped and provided whole blood samples for RNA Sequencing. Cluster analysis was used to divide the subjects into groups by gene expression signature. Across-cluster differential gene expression analysis and gene set enrichment analysis were performed, both using a false discovery rate (FDR) adjusted significance threshold of 0.05.

Results: There were two clusters (N1=23 and N2=17); 133 genes were differentially expressed between them. The top two most significant pathways were IFN-γ and IFN-α response (p <0.001), over expressed in group 2. 6 genes encoding targets of the transcription factor family E2F (p <0.001) were over-expressed in group 1. Targets of the transcription factor NF-kb (p <0.001) when activated by the cytokine Tumor Necrosis Factor-α were over-expressed in group 2. Genes up-regulated and down-regulated by kRas protein activation were also found to be significantly enriched (both p = 0.006) with expression higher in group 2 for 7 of the 9. Clusters did not differ by age, gender, race or body mass index.

Conclusions: Our results identify significant variation in basal immune state in depression, and that innate immunity, in particular, the interferon response, accounts for the difference. This result supports the dimensional nature of inflammation in depression.

Supported By: NIMH, CTSA, Institutional Funding

Keywords: Depression, Inflammation, functional genomics

302. Sleep Onset Insomnia, Daytime Sleepiness and Sleep Duration in Relationship to Toxoplasma gondii IgG Seropositivity and Serointensity

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Background: Toxoplasma gondii (T. gondii), a protozoan parasite with an intrinsic capacity to produce dopamine, infects central nervous tissue, and is kept in relative dormancy by immune defenses in immunocompetent hosts. T. gondii has been previously associated with mental illness, suicidal behavior and risk for car accidents, previously shown to be also triggered or exacerbated by sleep disruption, in particular insomnia. Our overarching hypothesis is that sleep disruption could mediate the link between T. gondii and psychiatric illness risky behaviors, potentially via dopaminergic or immune activation mechanisms. As a pre-requisite to support our overarching hypothesis, links between T. gondii and sleep disruption were examined in a convenience sample of Old Order Amish.

Methods: Sleep questionnaire data was analyzed from the Amish Wellness Study (N = 2031; mean age = 43.96, SD: 17.03; 1182 women (58.19%) and 849 men (41.80%). These included self-reported measures of sleep latency, duration, and daytime sleepiness [(Epworth Sleepiness Scale (ESS)]. ELISAs were used to measure T. gondii IgG seropositivity and serointensity, and plasma neopterin concentration, an indicator of inflammation.

Results: T. gondii seropositivity was not significantly associated with any of the sleep latency variables or ESS, using logistic and linear regressions. In males (after adjustment for age group and gender), we identified a statistical trend towards lower sleep duration in seropositive men (p = 0.07).

Conclusions: In conclusion, it is unlikely that insomnia mediates behavioral effects of T. gondii. Trending gender differences in associations between T. gondii and sleep duration may be worth further investigation.

Supported By: The University of Maryland, Joint Institute for Food Safety and Applied Nutrition and the U.S. Food and Drug Authority (U.S. FDA) through their cooperative agreement FDU.001418 (PI Postolache), and with additional funding from the P30DK072488 NIDDK (NORC – child project developmental grant Postolache) from the National Institutes of Health.

Keywords: Insomnia, Toxoplasma gondii, Sleep Duration, Old Order Amish, Epworth Sleepiness Scale

303. Moderation of the Relationship between T. gondii Seropositivity and Impulsivity in Younger Men by the Phenylalanine-Tyrosine Ratio

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Supported By: The University of Maryland, Joint Institute for Food Safety and Applied Nutrition and the U.S. Food and Drug Authority (U.S. FDA) through their cooperative agreement FDU.001418 (PI Postolache), and with additional funding from the P30DK072488 NIDDK (NORC – child project developmental grant Postolache) from the National Institutes of Health.

Keywords: Insomnia, Toxoplasma gondii, Sleep Duration, Old Order Amish, Epworth Sleepiness Scale
Thursday Abstracts

Psychiatry, Physical Medicine and Rehabilitation, and Neurology; Military and Veteran Microbiome: Consortium for Research and Education (MVM-CoRE), 4Mood and Anxiety Program, University of Maryland School of Medicine; Saint Elizabeths Hospital Psychiatry Residency Training Program, 5Mood and Anxiety Program, University of Maryland School of Medicine; 6College of Nursing, University of South Florida; 7Department of Psychiatry, Martin-Luther-University of Halle-Wittenberg, 8Division of Psychiatry and Behavioral Medicine, College of Human Medicine, Michigan State University, 9Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC); University of Colorado, Anschutz Medical Campus, Departments of Psychiatry, Physical Medicine and Rehabilitation, and Neurology; Military and Veteran Microbiome: Consortium for Research and Education (MVM-CoRE); Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder; Department of Physical Medicine and Rehabilitation and Center for Neuroscience, University of Colorado, Anschutz Medical Campus, 10Mood and Anxiety Program, University of Maryland School of Medicine; Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC)

**Background:** We previously reported that Toxoplasma gondii (T. gondii) seropositivity is associated with higher impulsivity in younger men. It was reported that dopaminergic and serotonergic signaling regulate impulsivity, and T. gondii produces dopamine and induces changes in monoamine precursor metabolism. We recently reported that phenylalanine tyrosine ratio interacts with T. gondii seropositivity in predicting trait aggression. We now investigated if blood levels of dopamine and serotonin precursors or the tryptophan metabolite kynurenine moderate the T. gondii – impulsivity association.

**Methods:** In 951 psychiatrically healthy participants, trait impulsivity scores were obtained from Disinhibition subscale of the Sensation Seeking Scale-V. The impulsivity scores were related to T. gondii IgG seropositivity and intersected with categorized levels of phenylalanine (Phe), tyrosine (Tyr), Phe: Tyr ratio, kynurenine (Kyn), tryptophan (Trp) and Kyn:Trp ratio in interaction with age and gender. Statistical methods included ANCOVA with bivariate post-hoc Tukey tests.

**Results:** Only younger T. gondii-positive men with a high Phe:Tyr ratio (i.e., the ratio fell in top 25th percentile) had significantly higher impulsivity scores (p<0.01). There were no significant associations in other demographic groups including older men, younger or older women. No significant effects or interactions were identified for Phe, Tyr nor for Kyn, Trp and their ratio.

**Conclusions:** Phe:Tyr ratio plays a moderating role in the association between T. gondii seropositivity and impulsivity in younger men. These results could potentially lead to individualized approaches to reduce impulsivity and contribute to new preventative approaches for violence (including self-directed), addiction, and improved academic occupational functioning.

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**Keywords:** Toxoplasma gondii, Impulsivity, phenylalanine, tyrosine, serotonin precursors

### 304. Immunological, Molecular and Behavioral Effects of LPS Induced Maternal Immune Activation

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**Background:** Maternal immune activation (MIA) by infection during pregnancy has been postulated to increased risk of neurodevelopmental sequelae in offspring. However, the mechanism by which MIA causes long-term behavioral deficits in the offspring is yet to be elucidated.

**Methods:** Pregnant Wistar rats were given sterile saline or lipopolysaccharide (LPS) (10 μg/kg; i.p.) on embryonic day 15. The first groups of animals were sacrificed at 6, 12, and 24 h after vehicle or LPS injection. Amniotic fluid, placenta, and fetus brains were collected to measure levels of oxidative stress, cytokines, matrix metalloproteinase (MMP), blood-brain barrier (BBB) and placenta barrier integrity (PBI). The second groups of young adults were subjected to different behavioral paradigms.

**Results:** The LPS significantly increased the MMP-2 and MMP-9 in amniotic fluid and fetus brain with simultaneous increase in oxidative stress markers and antioxidant enzyme levels. In fetus brain (n=6) levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-18, INF-γ, M-CSF, MIP-1α, MIP-3α and erythropoietin increased at 24 h after MIA induction. LPS challenge also elevated oxidative stress markers with simultaneous increase in antioxidant levels in fetus brain. We also observed BBB breakdown and PBI after MIA. Intriguingly, we found that LPS treated young animals (n=10) showed alteration in behavior as analyzed by different behavioral paradigm. Statistical package for the social science version 20.0 was used for statistics.

**Conclusions:** Data from this study strongly suggests that long-term behavioral alteration and immune activation may involve MMP levels in MIA. Further investigating MMP modulation may provide clinically relevant translational approach to understand MIA.

**Supported By:** The Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHHealth), National Institute for Molecular Medicine (INCT-MM) and Center of Excellence in Applied Neurosciences of Santa Catarina
305. Interaction of Cortisol and Cytokines in Chronic Patients with Schizophrenia: Relationship to Psychopathology and Cognition

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**Background:** The bilateral communication between the immune and neuroendocrine systems plays an essential role in modulating the adequate response of the hypothalamic-pituitary-adrenal (HPA) axis to the stimulatory influence of cytokines and stress-related mediators. Growing evidence suggests that neuro-immune-endocrine crosstalk may be impaired in schizophrenia. Although both cortisol and cytokines occur at abnormal levels in schizophrenia patients, their interactions have been under-examined.

**Methods:** We therefore compared serum cortisol, interleukin (IL)-2, IL-6, and IL-8 levels in 164 chronically medicated schizophrenia patients and 62 healthy controls. We correlated these serum levels within these subject groups with each other and with clinical symptoms assessed according to the Positive and Negative Syndrome Scale (PANSS).

**Results:** Compared to the control group, the schizophrenia patients had significantly higher cortisol and IL-6 levels. The patients also showed a significant negative correlation between cortisol and IL-2, but a significant positive association between cortisol and IL-6 or IL-8. The interaction of cortisol and IL-2 was linked to positive and depressive symptoms of schizophrenia. In addition, correlation analyses showed a significant negative association between IL-2 and the PANSS positive symptom subscore, but positive between IL-2 and negative symptom subscore. Also, correlation analyses showed a significant negative association between cortisol and the PANSS negative symptom subscore, but positive between cortisol and the PANSS cognitive factor subscore.

**Conclusions:** An interaction between cytokines and cortisol may be implicated in the pathophysiology of chronic schizophrenia. In particular, the interaction of cortisol and IL-2 was linked to clinical phenotypes of schizophrenia.

**Keywords:** Schizophrenia, psychoneuroimmunology, Psychopathology, cognition, Cytokine

306. Inflammatory Biomarkers in Psychosis

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**Background:** Immunological and inflammatory theories of schizophrenia exist, and multiple studies show increased cytokines, especially IL-6, in all phases of psychosis. In this study we investigated potential contributors of IL-6 elevations in psychosis: nutritional factors (vitamin D3) and immune biomarkers (CRP and LPS antibodies).

**Methods:** We compared vitamin D3, C-reactive protein, LPS antibodies and IL-6 levels in children, adolescents and young adults with psychosis (n = 43), clinically high risk for psychosis (n = 18) and unaffected comparison controls (n = 30). Participants were diagnosed by a psychiatrist using a structured interview, the MINI-Neuropsychiatric Interview. 25 (OH)D3 was measured in serum using chemiluminescent microparticle immunoassay, and LPS antibodies, CRP and IL-6 levels were measured using ELISA assays.

**Results:** There is a significant difference in IL-6 levels between the psychosis group and the unaffected comparison controls, (p<.042), OR 3.7 (confidence interval 1.05-13.05). Our data show that in the psychosis group, IL-6 is positively correlated with LPS antibodies (p<.0325) and CRP (p<.0001). In the psychosis group, IL-6 is negatively correlated with vitamin D3.

**Conclusions:** Our findings show a significant correlation between IL-6, CRP, LPS antibodies and vitamin D deficiency in psychosis, suggesting multiple pathways to IL-6 elevation, and multiple potential strategies for risk mitigation. Collectively these inflammatory biomarkers support further evidence of an immunological pathophysiology in psychosis, and may contribute to gut and blood brain barrier dysfunction. Further studies that investigate gut barrier integrity and BBB dysfunction in this population may shed light on this mechanism, as well as the potential efficacy of vitamin D supplementation.

**Supported By:** AACAP

307. Potential Biomarkers of Impending Schizophrenia Relapse: Exploratory Analysis of a Randomized, Double-Blind, Placebo-Controlled, Phase-3 Study of Paliperidone Palmitate 3-Month Formulation

Srihari Gopal, Maura Furey, Derrek Hilar, Hartmut Kolb, Ziad Saad, Adam Savitz, and Gallen Triana-Baltzer

Janssen Research & Development, LLC

**Background:** The need to predict relapse in schizophrenic patients for early intervention is critical. Here we explored biomarkers in patients who relapsed (paliperidone palmitate 3-monthly [PP3M] or placebo) compared to biomarkers in patients who remained stable during a randomized, double-blind (DB), multicenter, phase-3 study.

**Methods:** Patients received PP1M (50-150 mg eq.) during 17-week transition phase, followed by PP3M (3.5x stabilized dose of PP1M) during 12-week maintenance phase. Stabilized patients were randomized (1:1) to fixed dose of PP3M (175-525 mg eq.) or placebo during the DB phase. Blood was sampled every 4 weeks from week 17 to study end for biomarker measurement (leptin, adiponectin, mature BDNF, IGF1, cortisol, CRP, TNFα, IL1β, IL6, IL6R, IL10, gp130, IL1RA).
308. Decision-Making under Risk in Obsessive-Compulsive Disorder and Anxiety: A Cumulative Prospect Theory Model

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Background: Everyday decision-making in patients with obsessive-compulsive disorder (OCD) and anxiety is likely influenced by excessive fear and worry. However, the impact on specific cognitive aspects of decision-making, as operationalized in neuroeconomic models, has not previously been examined.

Methods: Fifty-nine participants (10 obsessive-compulsive disorder (OCD); 15 generalized anxiety disorder; 14 social anxiety disorder; 20 healthy controls) performed a two-gamble decision-making choice task. Each gamble included a visual representation of the probabilities of gaining and/or losing points. Performance was modeled within Cumulative Prospect Theory framework, a prominent model for decision-making under risk (Tversky & Kahneman, 1992). In this paradigm, an S-shaped valued function models diminishing sensitivity for increasing gains/losses and loss-aversion. Additionally, an inverse S-shaped probability function over-weights small probabilities and under-weights large probabilities. Using a non-linear regression model, the four parameters represented in these functions were estimated for each participant, to generate a close fit of his/her performance on the task.

Results: OCD patients were found to have lower value discrimination than controls (p=.001), while neither of the other anxiety groups differed from healthy controls on any of the estimated parameters.

Conclusions: These findings suggest that lower value discrimination may contribute to impaired decision-making in OCD patients. This may be linked to the dysfunctional reward processing and anhedonia often demonstrated in these patients. The results support differentiation in decision-making between OCD and the two anxiety disorders. They also suggest that models utilizing Cumulative Prospect Theory may help to delineate aspects of decision-making that are altered in psychiatric disorders.

Keywords: Anxiety Disorder, Obsessive Compulsive Disorder (OCD), Decision Making

309. ARTIST: A Fully Automated Algorithm for Removing Artifacts in Single-Pulse TMS-EEG Data

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Stanford University

Background: Concurrent single pulse TMS-EEG (spTMS-EEG) data suffer from enormous stimulation-induced artifacts, posing significant challenges to the extraction of neural information. Developing an automated algorithm to remove artifacts would reduce bias from human influence and decrease processing time. While there has been a recent push to develop automated artifact rejection methods for standard EEG data, to our knowledge no such methods dedicated to spTMS-EEG data have been reported.

Methods: We present a fully automated algorithm, termed Automated aRTIfact rejection for Single-pulse TMS-EEG Data (ARTIST), for spTMS-EEG artifact rejection. This algorithm first decomposes the spTMS-EEG data into statistically independent components (ICs), and then learns a pattern classifier to identify artifact components based on knowledge of the spatio-temporal profile of both neural and artefactual activity.

Results: ARTIST achieved an IC classification of 95% across a large number of spTMS-EEG data sets (n = 90 stimulation sites) when compared to manual artifact rejection. This accuracy was retained across stimulation sites, subjects, and populations. Moreover, the auto-cleaned and hand-cleaned data yield similar group TMS-evoked potential (TEP) waveform, as shown by the strong within-subject correlations attained for the TEP time series between hand-cleaned and ARTIST-cleaned data (p < 0.01).

Conclusions: This algorithm will greatly improve the precision and processing time of TMS-EEG experiments, allowing the analysis of the large-scale TMS-EEG connectome data sets to be completed within a short period of time. This also opens up the potential for near real-time processing of data, which could lead to monitoring of ongoing states and closed loop applications.

Supported By: Cohen Veterans Bioscience and the Stanford Neurosciences Institute; National Natural Science Foundation of China under Grants 61403144; Alpha Omega Alpha Postgraduate Research Award

Keywords: TMS-EEG, Artifact Rejection, Independent Components Analysis

310. Simultaneous [18F]Flumazenil-Positron Emission Tomography and GABA-Magnetic Resonance Spectroscopy in Adults with Autism and Healthy Volunteers

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Stanford University
**Background:** Dysfunction of the GABA neurotransmission system is one of the most accepted pathophysiologic mechanisms for autism spectrum disorder (ASD). This pilot study aims at demonstrating the GABA receptor binding potentials and GABA levels in high-functioning adults with ASD are distinctly different from age-matched typically-developing controls (TD).

**Methods:** Participants were scanned on GE SIGNA simultaneous PET/MR system. [18F]flumazenil was used as radiotracer for the GABAA receptors. During PET data acquisition, MR T1 and T2-weighted structural sequences were acquired. For the MRS measurements of GABA, MEGA-SPECIAL (TE=80ms, TR=2s) was performed on the bilateral thalami. A reference tissue model (ichise model; MRTM0) was used to calculate binding potentials (BPND) with pons as the reference region. The MEGA-SPECIAL edited spectrum was obtained by subtracting the editing OFF spectrum from the editing ON spectrum. GABA level was estimated from the integrated 3ppm peak area in the edited spectrum divided by the Cre peak area.

**Results:** Six healthy male volunteers and two adults with ASD were scanned. Highest uptake was observed in the neocortical regions and limbic system, intermediate in the cerebellum, thalami and basal ganglia, and low uptake in the brainstem. Significant differences in BPND were found in the caudate nucleus (1.5 in TD vs. 1.9 in ASD; p = .035) and brainstem (0.4 in TD vs. 0.6 in ASD; p = .043). The mean thalamic GABA/Cre ratio in TD (7.9) is higher than ASD (5.8).

**Conclusions:** GABAA receptor densities appear to be higher in high-functioning adults with ASD, as compared to TD. Further studies are warranted to confirm this finding.

**Supported By:** K08MH111750

**Keywords:** GABA, Autism Spectrum Disorder, PET imaging, MRS

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**311. DLPFC Neuroplasticity and Working Memory Performance in Alzheimer’s Disease**

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**Background:** Working memory deficits are known in Alzheimer’s disease (AD). Dorsolateral prefrontal cortex (DLPFC) plasticity is important for working memory. The aim of this study is to assess DLPFC plasticity in vivo and its relationship to working memory in AD.

**Methods:** Participants with AD and healthy adults 65 years or older were enrolled. Paired Associative Stimulation (PAS) combined with electroencephalography (EEG) was used to assess DLPFC plasticity. PAS-induced potentiation of cortical evoked activity (CEA) over the DLPFC was used as a measure of plasticity. The N-Back task (1 and 2-back) was used to assess working memory.

**Results:** 33 participants with AD (female = 17, mean Age = 76.5, SD = 6.2) and 18 healthy adults (female = 10, mean Age = 75.6, SD = 5.5) were enrolled. Participants with AD had impaired potentiation of CEA (mean = 1.18, SD = 0.25) compared to healthy adults (mean = 1.40, SD = 0.34) (Cohen’s d = 0.78, p = 0.010). They were also impaired on 1-back (Cohen’s d = 1.87, p < 0.001) and 2-back (Cohen’s d = 2.55, p < 0.001) performance. Finally, potentiation of CEA was positively correlated with working memory performance on 1-back (Pearson’s correlation, r = 0.34, p=0.016) and 2-back (Pearson’s correlation, r = 0.42, p=0.004) conditions.

**Conclusions:** This is the first study showing impaired DLPFC plasticity and its relationship to working memory in patients with AD. These findings could lead to the development of novel biomarkers based on DLPFC plasticity as well as novel treatment targets for AD.

**Supported By:** W. Garfield Weston Foundation, Center for Addiction and Mental Health Foundation, Canadian Institute of Health research, Canada Foundation for Innovation, NARSAD Young Investigator Grant from the Brain and Behavior Foundation

**Keywords:** Neuroplasticity, Alzheimer’s Disease, Dementia, Paired Associative Stimulation, Dorsolateral Prefrontal Cortex

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**312. Culturally Sensitive Cognitive Stress Test is Related to Alzheimer’s Disease (AD) Signature Regions on MRI**

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**Background:** Culturally sensitive cognitive measures able to detect deficits in persons with incipient AD is a priority in the field due to the growing elderly Hispanic population. The Loewenstein-Acevedo Scales of Semantic Interference and Learning (LASSI-L), is a novel assessment with high levels of sensitivity and specificity that has been validated in Spanish. This study aims to relate cognitive performance on the LASSI-L to changes in MRI brain volumes in English-speaking (ES) and Spanish Speaking (SS) older adults.

**Methods:** We studied 30 ES participants and 21 SS participants diagnosed with amnestic Mild Cognitive Impairment (aMCI) who had both the LASSI-L and MRI brain scans. 43 ES and 20 SS cognitively normal (CN) participants were used as a control. Performance on the LASSI-L indices was compared to brain volumes in regions vulnerable to AD pathology.

**Results:** LASSI-L Cued B2 recall is associated with volume loss in biologically relevant regions for both ES and SS aMCI participants. The LASSI-L discriminates aMCI from CN participants in both ES and SS groups. ES aMCI participants seem to have more volume loss in the hippocampus than SS MCI patients. While ES aMCI and ES CN can be readily differentiated by MRI, this is not true for the corresponding SS groups.
Conclusions: LASSI-L offers a well-validated and effective memory measurement paradigm that has shown to be a cross-culturally sensitive in diagnosing aMCI and CN Hispanic elderly. The Cued B2 measure is related to brain volumes in AD sensitive regions in both SS and ES with aMCI.

Supported By: R01, P01

Keywords: Alzheimers, MCI, Aging, Spanish, LASSI-L

313. Cortical Surface Based Threshold Free Cluster Enhancement and Cortex-Wise Mediation

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Background: Threshold-free cluster enhancement (TFCE) is a sensitive means to incorporate spatial neighborhood information in neuroimaging studies without using arbitrary thresholds. The majority of methods have applied TFCE to voxel-wise data. The need to understand the relationship among multiple variables and imaging modalities has become critical.

Methods: We propose a new method of applying TFCE to vertex-wise statistical images as well as cortex-wise (either voxel- or vertex-wise) mediation analysis. We present TFCE_mediation that can be used for cortex-wise multiple regression analysis with TFCE, and additionally cortex-wise mediation using TFCE. The toolbox are written using free software packages, and they are publicly available (https://github.com/trislett/TFCE_mediation). We validated TFCE_mediation in healthy controls from two independent multimodal neuroimaging samples (N=199; N=183).

Results: We found a consistent structure-function relationship between surface area and the first independent component (IC1) of the N-back task, that white matter fractional anisotropy is strongly associated with IC1 N-back, and that our voxel-based results are essentially identical to FSL randomise (all PFWE<0.05).

Using cortex-wise mediation, we showed that the relationship between white matter FA and IC1 N-back is mediated by surface area in the right superior frontal cortex (PFWE<0.05). We also demonstrated this same mediation model is present using vertex-wise mediation (PFWE<0.05).

Conclusions: Cortex-wise analysis with TFCE provides an effective analysis of multimodal neuroimaging data. Further, cortex-wise mediation analysis may identify or explain a mechanism that underlies an observed relationship among a predictor, intermediary and dependent variables in which one of these variables are assessed at a whole brain scale.

Supported By: CIHR, BMBF, DFG

Keywords: Cortical surface area, Cortical Thickness, Diffusion Tensor Imaging (DTI), Threshold-free Cluster Enhancement (TFCE), Mediation Analysis

314. Hedonic Capacity as a Predictor of ADHD and Treatment Response in Depressed Patients

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Background: Depression has become a major public health concern as rates continue to increase and have become among the leading cause of disability and subsequent death. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. A core symptom of depression, anhedonia, is associated with poorer treatment response in patients treated with traditional antidepressants. Thus, the aim of this study is to determine predictive factors and clinical features associated with the development of treatment-resistant depression (TRD).

Methods: Data is being collected from consecutive referrals to a tertiary-care mood and anxiety clinic 160 subjects have been enrolled in the study to date. Diagnosis was established by using the Mini International Neuropsychiatric Interview Plus 5.0.0 and a semi-structured interview by the treating physician. One-way analysis of variance and t-tests were undertaken to examine predictive factors related to the development of TRD.

Results: Preliminary results suggest that 34% of patients referred for TRD had untreated ADHD of which 48% suffered with chronic anhedonia. The number of failed psychiatric medications (p<0.001), and past SSRI failures (p<0.032) were predictive of ADHD in patients with TRD, with SSRI failure predicting chronic anhedonia (p<0.002).

Conclusions: These results support ADHD as a significant risk factor for the development of TRD, with chronic (trait) anhedonia or low hedonic tone providing a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs.

Keywords: Hedonic capacity, Dopamine, Treatment resistance, Depression

315. Retinal Vascular Photography as a Window into the Cardiovascular Burden of Adolescent Bipolar Disorder

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Background: Cardiovascular disease is excessive in bipolar disorder (BD) and occurs up to 17 years prematurely. The cardiovascular burden in BD exceeds what can be explained by traditional cardiovascular risk factors (CVRFs), lifestyle, and/or medications. This study examines retinal vascular photography, a proxy for cerebral microvascular pathology,
in relation to CVRFs and peripheral microvascular function among adolescents with BD.

**Methods:** Subjects were 30 adolescents with BD and 32 healthy controls (HC). Retinal photography was conducted using a Topcon TRC 50 DX, Type IA camera, following pupil dilation. Retinal arteriolar and retinal venular caliber was measured, from which the arterio-venular ratio (AVR) was computed. Inter-rater reliability for all measured arterioles and venules ranges from interclass correlation 0.839-0.966 (almost perfect agreement). All measures were conducted masked to participant diagnosis. CVRFs were measured via fasting blood draw, and peripheral microvascular function was measured via peripheral arterial tonometry.

**Results:** AVR was not significantly different between groups (BD: 0.65±0.08, HC: 0.62±0.08; Cohen’s d=0.18, p=0.103). Higher diastolic blood pressure was associated with lower (worse) AVR in BD (r=−0.454, p=0.012) but not HC (r=−0.145, p=0.430). Similarly, in BD only, higher (better) endothelial function was associated with higher AVR (r=−0.375, p=0.041). Hierarchical regression models confirmed that, independent of covariates, retinal vascular caliber significantly predicted diastolic blood pressure and endothelial function in BD.

**Conclusions:** Retinal vascular caliber is associated with blood pressure and endothelial function in BD adolescents, independent of other predictors. Retinal photography may offer unique insights regarding the cardiovascular burden of BD. Larger longitudinal studies are warranted.

**Keywords:** Bipolar Disorder, Cardiovascular Disease, Retinal Photography, Adolescents

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**Background:** Multiple neuroimaging studies have extensively reported on trajectories of brain development. These studies have undoubtedly advanced our understanding of typical and atypical brain development. However, data and knowledge generated from these studies has not been summarized to be easily accessible to both researchers and non-researchers. We report a novel web-based visual and analytical search engine platform able to compute regional brain trajectories as well as display graphical and statistical results to users.

**Methods:** T1-weighted brain scans from 303 healthy individuals aged 5-18 years were acquired from the NIH pediatric repository (http://www.pediatriccmri.nih.gov). Scans were pre-processed using the Freesurfer software and regional brain volumes calculated. A novel analytical software platform and search engine were developed using Python and Django software/web frameworks.

**Results:** The resulting software tool was able to store, analyze and visualize regional brain development trajectories. Figure 1, shows a search engine able to query a specific brain region and the analytical software is able to fit regression lines, calculate statistical measures, and display results to users through the web.

**Conclusions:** Our soon to be launched web-based software tool will allow storage of large volumes of pre-processed neuroimaging measures coupled with computation of brain development trajectories. In future, information from previously published studies will be incorporated to the platform. We envisage brain search being a platform where researchers and non-researchers can obtain summarized analytical and peer reviewed evidence on brain trajectories.

**Keywords:** brain maturation, brain development, Neuroimaging, Big Data Analysis, Big data

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**317. Screening for Auto-Antibodies with Antidepressant Medications Using Glomerular Proteomic Microarray Arrays: Findings from CoMed Clinical Trial**

Bharathi Gadad, Manish Jha, Yun Yun, Min Kim, Guanghua Xiao, Michael Emslie, Thomas Carmody, and Madhukar Trivedi

University of Texas Southwestern Medical Center at Dallas

**Background:** Up-regulation of inflammatory response has been well established in Major Depressive disorder (MDD). However, studies on immune activation by generation of antibodies with the antidepressant medications are limited. To investigate the prevalence and clinical significance of a spectrum of autoantibodies with antidepressants medications like SSRIs and SNRIs in Combination of Medications to Enhance Depressive Outcomes (Co-MED), a 3-arm treatment clinical trial.

**Methods:** Plasma samples from 280 participants at pre and post-treatment were analyzed on autoantigen microarray super panel, GenePix 6 (128 autoantigens for IgG and IgM and various internal controls). The autoantigens in this panel include most of nuclear antigens, cytoplasmic antigens, membrane antigen, phospholipid antigens, as well as some novel autoantigen identified so far for most of the autoimmune related diseases. Pairwise comparison were employed to assess 128 autoantigens with regard to pre/post treatment and based on the treatment groups.

**Results:** Among all the 128 super panel of auto-antigens, with pre and post-treatment, 79 IgG autoantibodies were identified as positive hits that formed 4 clusters that showed differential expression. Based on the antidepressant medications by treatment arm we found elevated levels of Aquaporin-4-IgG and Complement C1Q-IgG antibodies and no IgM autoantibodies. Multivariate analyses were done with regard to response (Quick Inventory of Depressive Symptoms-Self Rated (QIDS-SR) > 50% reduction) and remission (QIDS-SR < 5).

**Conclusions:** Antidepressants irrespective of SSRIs and SNRIs regulate the expression of Aquaporin-4 and Complement C1Q IgG antibodies, suggesting that both these autoantibodies are required for the mechanism of action of these medications.

**Supported By:** Hersch Foundation

**Keywords:** Major Depressive Disorder (MDD), Autoantibodies, Microarray, Inflammation, Antidepressants
318. Reliability of Transcranial Magnetic Stimulation EEG Evoked Potentials

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Background: Single-pulse Transcranial Magnetic Stimulation (TMS) coupled with EEG yields evoked potentials (TEPs) thought to reflect therapeutically relevant neurocircuitry that could inform future clinical biomarkers. However, to our knowledge, no studies have rigorously measured the test-retest reliability of TEPs beyond simple correlation.

Methods: Healthy control subjects from the Stanford University community were stimulated with single-pulse TMS to the left dorsolateral prefrontal cortex (DLPFC) over 6 weeks (30 treatments). Each week, subjects completed the Beck Depression Inventory (BDI) and a novel scale, the Coplan Emotional Theory of Mind scale, which captures an individual’s perception of self and others - phenomena putatively related to the RPFC.

Results: Twelve of 23 subjects responded to the BDI. Starting BDI scores predicted BDI response; patients with higher BDI scores were less likely to respond (p=.05). Persistence of high Coplan scores was associated with non-BDI response. For non-responders, BDI scores dropped significantly more than Coplan scores: [S(C)×Week effect: F(5, 50)=4.74, p=.001].

Conclusions: Most rTMS studies focus on the DLPFC to the exclusion of medial and rostral areas of the PFC. Recent research on the RPFC demonstrates the relationship between this area, self-reflection, and the default mode network (DMN). Our analysis indicates that only ~50% of patients respond to traditional DLPFC rTMS, and that non-response is associated with continued disturbances in self-reflection and perception of others. Future studies should focus on the application of rTMS to areas within the RPFC such as Brodmann’s area 10 (BA10).

Keywords: HF-rTMS, Theory of Mind, Psychometrics, Mood disorders, Rostral Prefrontal Cortex

319. Depressive Response and the Rostral PFC: A Novel Assessment of Emotional 'Theory of Mind' Changes Following rTMS

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Background: Major depressive disorder (MDD) warps an individual’s sense of self and how they feel they are perceived by others – phenomenological concepts related to an individual’s emotional ‘theory of mind’. The rostral prefrontal cortex (RPFC) is associated with reflective thought processes such as self-knowledge and perception of others. The relationship between this area, depressive symptomatology, and depressive response remains understudied.

Methods: Twenty-three MDD patients received repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsolateral prefrontal cortex (LDPFC) over 6 weeks (30 treatments). Each week, subjects completed the Beck Depression Inventory (BDI) and a novel scale, the Coplan Emotional Theory of Mind scale, which captures an individual’s perception of self and others - phenomena putatively related to the RPFC.

Results: Twelve of 23 subjects responded to the BDI. Starting BDI scores predicted BDI response; patients with higher BDI scores were less likely to respond (p=.05). Persistence of high Coplan scores was associated with non-BDI response. For non-responders, BDI scores dropped significantly more than Coplan scores: [S(C)×Week effect: F(5, 50)=4.74, p=.001].

Conclusions: Most rTMS studies focus on the DLPFC to the exclusion of medial and rostral areas of the PFC. Recent research on the RPFC demonstrates the relationship between this area, self-reflection, and the default mode network (DMN). Our analysis indicates that only ~50% of patients respond to traditional DLPFC rTMS, and that non-response is associated with continued disturbances in self-reflection and perception of others. Future studies should focus on the application of rTMS to areas within the RPFC such as Brodmann’s area 10 (BA10).

Keywords: HF-rTMS, Theory of Mind, Psychometrics, Mood disorders, Rostral Prefrontal Cortex

320. Studying Mood in Those who Do Not Get Sick: Nonlinear Dynamics of Mood Regulation in First-Degree Healthy Relatives of Bipolar Disorder Patients

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Background: Mood regulation is a complex and poorly understood process. Nonlinear techniques offer new tools with which to quantify, model, and attempt to predict the behavior of complex systems. The aim of this study is to analyze mood variability in those who do not get sick (first-degree healthy relatives of bipolar disorder) and compare it with healthy controls (HC) and bipolar patients (BD).

Methods: We recruited 30 HC; 30 euthymic BD subjects, and 25 first-degree healthy relatives of patients with BD. Participants underwent a psychiatric evaluation and a SADS-L. Participants rated their mood, anxiety and energy levels using a visual analog scale, over a three month period. Information on sleep and life events was also recorded. We analyzed the data using Box-Jenkins time series and performed entropy calculations.

Results: We analyzed 14,196 datapoints. Self-ratings for mood, anxiety and energy were normally distributed in all groups. Autocorrelation functions for mood in all groups are governed by the ARIMA (1,1,0) model, which means that current values in the series are related to one previous point only. Entropy for mood was higher in healthy controls (1.47 - 0.33) compared to both BD (1.04 - 0.68) and healthy relatives (1.07 -0.68) [F(1, 73)= 3.92; p < 0.05].
Conclusions: Mood can be considered a memory stochastic process in HC, euthymic BD and their healthy first-degree relatives. Healthy relatives’ measurements are “in between” those of BD and HC, which provides further insight into the nature of mood regulation in BD and supports the utility of nonlinear analyses in Psychiatry.

Keywords: Mood, entropy, nonlinear

321. Watching Synapses in Action: From Assaying Synaptic Function to Drug Discovery

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Background: Synaptic deficits in function and number are at the core of psychiatric and neurodegenerative diseases. The only way to alleviate the disease symptoms is by repairing the synaptic deficits and restoring functional connectivity of defined neuronal circuits. This requires monitoring and controlling the activity of thousands of synapses. Recent technological advances in the form of genetically-encoded sensors of neuronal activity, optogenetic actuators, and novel imaging methodologies make it now possible to record and manipulate the activity of neural circuits at exquisite spatiotemporal precision. Here we showcase our efforts towards bringing these breakthrough technologies in our drug discovery programmes.

Methods: In a novel drug-screening platform, using rat neuronal cultures, we employ genetically-encoded sensors that allow us to record in real time synaptically localized Ca2+ events, vesicle exo/endoctosis, and release of various neurotransmitters. We stimulate the cultures either by using a pair of electrodes or using channelrhodopsin in an all-optical approach. Using advanced image analysis software, we extract information about the activity of individual synapses within a population.

Results: We employ this strategy to study the synaptic underpinnings of the cognitive and mnemonic frailty in Alzheimer’s disease and to find molecules that repair synaptic deficits. In particular, we show data in the context of discovering novel modulators of synaptic plasticity.

Conclusions: In future, we will expand this technological approach to assay synaptic plasticity in human iPSC-derived neurons and ex vivo in model systems of Alzheimer’s disease. The technology is amenable for translational use in the context of any psychiatric disease.

Keywords: Alzheimer’s Disease, synaptic plasticity, calcium imaging, psychiatric disorders, in vitro

322. Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex: A Review of Methods and Utility in Psychiatry

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Background: Transcranial magnetic stimulation (TMS) constitutes a major addition to the armamentarium of non-invasive investigative and treatment techniques for psychiatry disorders. There is evidence pointing to the potential role of TMS to elucidate biological markers of psychiatric disorders. Compared to the motor cortex, there is less use of TMS for functional assessment of non-motor cortical regions of the brain despite therapeutic applications of TMS on DLPFC (a non-motor cortical area) in treat-resistant psychiatric disorders. Thus, we propose to review evidence on TMS paradigms focused on Dorsolateral Prefrontal Cortex (DLPFC) in major psychiatric disorders, and synthesize evidence on the application of TMS in neurobiological investigation underpinning these major psychiatry disorders especially neurocognitive functions.

Methods: A comprehensive literature search and review based on the PRISMA approach was carried out using the following MeSH terms- “TMS”, “TMS-EEG”, “DLPFC”, “TMS”, “EEG”, “Psychiatry disorders” and “Non-invasive brain stimulation”, “Neurocognitive”, “Functional outcome”

Results: There are known therapeutic applications of TMS on DLPFC (non-motor cortical area) in cases of treat-resistant psychiatric disorders. A number of TMS paradigms have been used to investigate the neurobiological processes underlining the phenotypic expression, delayed treatment response and neurocognitive outcome of psychiatric disorders. Results from TMS have implicated non-motor cortical regions (DLPFC) in the pathophysiology of major psychiatric disorders, that include the neurocognitive dysfunctions often seen in these disorders despite treatment.

Conclusions: The use of TMS on DLPFC supports its potential role in elucidating biological signature of psychiatric disorders, and the need to extend its use in investigative/translational Psychiatry, especially on the non-motor cortical regions.

Keywords: Dorsolateral Prefrontal Cortex, Neurocognitive, Non-motor cortex, Transcranial Magnetic Stimulation

323. Utilizing Smartphones to Collect Longitudinal Digital Phenotypes in Patients with Schizophrenia

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Background: Digital phenotyping, the moment-by-moment quantification of the individual-level human phenotype using data from digital devices as proposed by JP Onnela, holds the potential to bring a stream of real time objective behavioral and physiological data into psychiatric research. In our ongoing study, we utilize the Beiwe platform to assess the feasibility and validity of passive data (GPS, accelerometer, voice, call logs, and text logs, screen use) from the personal smartphones of patients with schizophrenia as well as its utility in predicting relapse.

Methods: Subjects are adults diagnosed with schizophrenia, currently in treatment at a state hospital. Subjects install Beiwe on their smartphone for three months. During this time Beiwe offers bi-weekly EMA surveys and constant passive data collection – up to one million data points per day via the phones many sensors.

Results: From data pooled from all subjects 17 to date, the total duration of minutes not using the phone shows a negative correlation with the warning signs scale for psychosis (p=.0001)
324. The Validity and Sensitivity of PANSS-6 in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study

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Background: We recently demonstrated that a six-item version of the Positive and Negative Syndrome Scale (PANSS-6: P1=Delusions, P2=Conceptual disorganization, P3=Hallucinations, N1=Blunted Affect, N4=Social withdrawal, N6=Lack of spontaneity/flow of conversation) may be a practical and psychometrically valid alternative to the full 30-item version (PANSS-30). The aim of the present study was to test the validity and sensitivity of PANSS-6 further via a reanalysis of data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

Methods: First, we tested the scalability of PANSS-6 and PANSS-30. Scalability is present when each symptom item in a rating scale provides unique information regarding syndrome severity. Subsequently, we tested the level of correlation between the total scores of PANSS-6 and PANSS-30 in order to determine whether PANSS-6 conveys similar information as PANSS-30. Finally, to test whether PANSS-6 was equally sensitive as PANSS-30 in detecting differences in antipsychotic efficacy, we compared the effect of the five antipsychotics studied in CATIE, using the total scores of PANSS-6 and PANSS-30 as outcomes.

Results: PANSS-6 was scalable, whereas this was not the case for PANSS-30. The total scores on PANSS-6 and PANSS-30 were highly correlated (Spearman coefficient=0.86 based on 5,081 ratings). PANSS-6 and PANSS-30 identified the same statistically significant differences in antipsychotic efficacy, namely that olanzapine was superior to risperidone (P-value PANSS-6 = 0.0003 & P-value PANSS-30 = 0.0003) and ziprasidone (P-value PANSS-6 = 0.0016 & P-value PANSS-30 = 0.0046).

Conclusions: PANSS-6 is a brief rating scale for schizophrenia that adequately measures symptom severity and antipsychotic efficacy.

Supported By: The Lundbeck Foundation (unrestricted research grant)

Keywords: Schizophrenia, Psychometrics, Rating scales, Antipsychotics

325. Clinical Utility Study Towards the Use of Continuous Wearable Sensors and Patient Reported Surveys for Relapse Prediction in Patients at High Risk of Relapse in Schizophrenia

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Background: Relapse in schizophrenia patients is preceded by warning signs of biological, sensory and clinical status that can be identified to enable early intervention and avoid relapse events. This study aimed to evaluate the feasibility of using remote-sensing devices and electronic patient-reported surveys to identify symptom exacerbation correlates and relapse in high-risk schizophrenia patients.

Methods: In this noninterventional observational study, patients (≥19 years) diagnosed with schizophrenia or schizoaffective disorder (DSM-5 criteria) were enrolled. Patients were provided with remote-sensing devices to monitor activity (Garmin vivofit fitness band, Vancipe patch), sleep (Philips Actiwatch Spectrum); smartphones (Ginger.io app) were used for patient-reported outcomes survey. Clinical assessments were performed bi-weekly. Patients were observed for relapse (PANSS total score, subscales) over a 4-month period.

Results: Total 28/40 patients completed study without relapse. Relapse occurred in 3 patients but only one patient was stable and had sufficient post screening data to establish a reference baseline for device analysis. The range of days each device utilized across all patients provided a maximum number of observable days for each patient-device combination. With this reference, significant data coverage and compliance was observed (Garmin: 97%, Philips: 94%, Weekly survey: 88%, Vancipe: 83% and Bi-Daily Survey: 82%).

Conclusions: Although observations from a single patient do not allow inference of significant correlations with relapse, this study demonstrated that mobile technology could be effectively utilized to monitor relevant schizophrenia symptoms, which could lead to earlier intervention strategies. The operational learnings may provide insights to conduct future studies.

Supported By: Janssen Research & Development, LLC

Keywords: Device, Relapse, Remote sensing, Schizophrenia

326. Clustering by Salience Network Activation to Emotional Faces Identifies a Transdiagnostic Subtype that is Associated with Specific Interoceptive Related Symptoms

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1University of Alabama at Birmingham, 2Janssen Research & Development

Background: Relapse in schizophrenia patients is preceded by warning signs of biological, sensory and clinical status that can be identified to enable early intervention and avoid relapse events. This study aimed to evaluate the feasibility of using remote-sensing devices and electronic patient-reported surveys to identify symptom exacerbation correlates and relapse in high-risk schizophrenia patients.

Methods: In this noninterventional observational study, patients (≥19 years) diagnosed with schizophrenia or schizoaffective disorder (DSM-5 criteria) were enrolled. Patients were provided with remote-sensing devices to monitor activity (Garmin vivofit fitness band, Vancipe patch), sleep (Philips Actiwatch Spectrum); smartphones (Ginger.io app) were used for patient-reported outcomes survey. Clinical assessments were performed bi-weekly. Patients were observed for relapse (PANSS total score, subscales) over a 4-month period.

Results: Total 28/40 patients completed study without relapse. Relapse occurred in 3 patients but only one patient was stable and had sufficient post screening data to establish a reference baseline for device analysis. The range of days each device utilized across all patients provided a maximum number of observable days for each patient-device combination. With this reference, significant data coverage and compliance was observed (Garmin: 97%, Philips: 94%, Weekly survey: 88%, Vancipe: 83% and Bi-Daily Survey: 82%).

Conclusions: Although observations from a single patient do not allow inference of significant correlations with relapse, this study demonstrated that mobile technology could be effectively utilized to monitor relevant schizophrenia symptoms, which could lead to earlier intervention strategies. The operational learnings may provide insights to conduct future studies.

Supported By: Janssen Research & Development, LLC

Keywords: Device, Relapse, Remote sensing, Schizophrenia
Background: Dysfunctions within the salience network, particularly regions of the anterior insula and dorsal anterior cingulate cortex (dACC), are common across anxiety and depression at rest and in response to emotional stimuli. These regions are also implicated in interoception, or the monitoring of one’s internal state. We tested whether a data-driven approach would identify relationships between profiles of salience network activation and specific symptoms related to salience network functions, including interoception, that would cut across current diagnostic boundaries. 

Methods: 664 individuals with a broad range of anxiety and depression symptom severity completed an emotional processing fMRI task. Activation to happy and threatening faces was extracted from key salience nodes (insula, dACC, and amygdala). Salience network based subtypes were then defined using k-means clustering on the extracted activation values. Regression models determined whether these subtypes differed on symptom factors based on the Depression Anxiety and Stress Scale.

Results: In preliminary analyses, clustering identified two distinct salience network based subtypes defined by hyper- and hypo-reactivity to emotional faces across all nodes. The hyper-reactive group was further characterized by greater severity on a factor reflecting heightened anxiety and altered interoception (e.g. heart racing, difficulty breathing; t=3.56, p=0.0004). No other differences were found in other symptom factors (all p’s>0.56).

Conclusions: Results suggest a novel subtype of affective psychopathology based on emotionally-probed salience network function and characterized by altered interoception and heightened anxiety. Salience network hyper-reactivity may serve as a transdiagnostic mechanism underlying misinterpretation of salient cues and avoidance of situations that generate interoceptive stimulus overload.

Supported By: NIMH NRSA F32MH108299 and NIMH grant R01MH101496

Keywords: Research Domain Criteria (RDoC), salience network, interoception, Anxiety, Machine learning

327. Startle Reactivity to Unpredictable Threat as a Psychophysiological Treatment Target for Fear-Based Anxiety Disorders

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Background: Heightened reactivity to unpredictable threat (U-threat) is a core individual difference factor underlying fear-based psychopathology. Little is known, however, about whether reactivity to U-threat is a stable marker of psychopathology or if it is malleable to treatment and/or reflects dynamic changes in symptoms. The aim of the study was to address these questions by examining differences in reactivity to U-threat before and after evidence-based treatment.

Methods: Seventy-two participants were assessed 12-weeks apart to measure stability and changes in reactivity to U-threat across time and treatment. Participants included those with principal fear-based (n=22) and distress/misery disorders (n=29), and a group of healthy controls (n=21). A well-validated threat-of-shock task was used to probe reactivity to U-threat and startle eyeblink potentiation was recorded to index defensive responding.

Results: At pre-treatment, individuals with fear-based disorders displayed greater startle potentiation to U-threat relative to controls and distress/misery patients (who did not differ; F(2, 69)=4.30, p<.05). From pre- to post-treatment, startle potentiation to U-threat decreased within patients and the magnitude of decline in startle correlated with the magnitude of decline in fear symptoms within treatment responders with principal fear disorders only (r=-.65, p<.01). For the controls, startle potentiation to U-threat across the two time points was highly reliable and stable.

Conclusions: Together, these results indicate that startle potentiation to U-threat maps onto the fear dimension, as it is elevated within fear patients and tracks changes in fear symptoms. Startle to U-threat may also reflect a mechanism underlying treatment response.

Supported By: R01MH101497

Keywords: Startle response, Anxiety Disorder, Distress, Treatment Response, Research Domain Criteria (RDoC)

328. Differential Developmental Impacts of Abuse and Neglect on Systems Engaged in Task Performance and Emotional Responding

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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). Abuse has been widely associated with increased threat responsiveness but the impact of neglect, and whether this is selective, is rather less clear.

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 subjective value representation including the...
329. Testing the Specificity of Executive Functioning Impairments in Adolescents with ADHD, ODD/CD and ASD

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**Background:** Attention-deficit hyperactivity disorder (ADHD), oppositional defiant/conduct disorder (ODD/CD) and autism spectrum disorder (ASD) are separate psychiatric conditions, yet they often co-occur. They are all associated with impairments in executive functions (EF). The specificity of impairments in EF to each condition remains relatively unexplored.

**Methods:** Four groups of 10-16 year olds; typically developing (TD; N=43), patients clinically diagnosed with ADHD (N=24), ODD/CD (N=26) and ASD (N=41) completed a GoNoGo and a Switch task, giving indices of inhibition, intra-subject response variability, response time, and flexibility. Parent-reported psychiatric symptom severity was measured using the Strengths and Difficulties Questionnaire (SDQ). Analysis of variance (ANOVA) explored group differences; co-variates included age, IQ, sex, SDQ conduct and hyperactive symptoms. Sensitivity analyses excluded a) those with IQ<70 (N=9) and b) ASD participants scoring above SDQ hyperactivity threshold (N=10).

**Results:** All clinical groups demonstrated worse inhibitory performance, and increased response variability compared to the TD group. The ADHD group had significantly longer response times than all other groups. Results remained significant with inclusion of co-variates and in sensitivity analyses, except for response variability, which was no longer significant after inclusion of co-variates. No group differences were found in flexibility.

**Conclusions:** A more impulsive response style was present across all clinical groups. A similar pattern was found for response variability, although co-variates may have contributed to group differences. Disorder-specific impairment was found for ADHD, which was characterised by longer reaction times. Results suggest impairment in inhibition and increased response variability may represent trans-diagnostic deficits that are associated with a number of diagnoses.

**Supported By:** NIHR; MRC

**Keywords:** Autism Spectrum Disorder, ADHD, Conduct Disorder, Executive Functioning, Impulsivity

330. A Principal Components Analysis of Depression and Anhedonia Scales: Illustrating the Heterogeneity of Depression

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¹NIH/NIMH, ²National Institute of Mental Health, ³University of Warwick

**Background:** Depression is a heterogeneous disorder with a variety of symptoms including depressed mood, anhedonia, and negative cognitive biases. Due to this heterogeneity, current depression rating scales address a number of symptoms that may be useful in translational approaches to depression research. Our aim in this analysis was to conduct an exploratory analysis to examine potential symptom components across rating scales. Identifying specific depressive symptom clusters may be useful in isolating associations with biomarkers that could facilitate understanding the biological underpinnings of depression.

**Methods:** Baseline ratings from 119 currently depressed inpatients participating in IRB-approved clinical trials were included in this analysis. Principal components analysis (PCA) was performed using varimax rotation with Kaiser normalization. Measures included in this PCA were the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Montgomery Asberg Depression Rating Scale (MADRS) and the Snaith-Hamilton Pleasure Rating Scale (SHAPS).

**Results:** The final model from the PCA contained 11 components. The components which explained the largest variance were anhedonia (comprised primarily from items on the SHAPS, 10.3%), self-criticism (comprised primarily from items on the BDI, 6.7%), suicide (6.4%), sadness (5.7%) and appetite (5.7%).

**Conclusions:** Depression rating scales capture a wide variety of symptoms. Anhedonia-specific scales, such as the SHAPS, may assess constructs as distinct from traditional clinician rated assessments such as the MADRS or HAMD. Collapsing symptoms across rating scales, using techniques such as PCA, may be helpful in understanding depressive symptomatology, and further, how specific symptom clusters may relate to particular biomarkers of depression.

**Supported By:** NIMH Intramural Program

**Keywords:** Depression, Principal Components Analysis, Rating Scales

331. Premorbid Social and Academic Adjustment Trajectories in Schizophrenia and Bipolar Disorder: A Transdiagnostic Cluster Analysis

Chi Chan¹, Megan Shanahan², Luz Ospina², Emmett Larsen², and Katherine Burdick³

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amygdala, ventromedial frontal cortex and posterior cingulate cortex during task trials. 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.

**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.

**Supported By:** Boys Town National Research Hospital

**Keywords:** RDoC, fMRI, child maltreatment, Abuse and Neglect, Emotion Regulation
Background: Schizophrenia and bipolar disorder exhibit within disorder heterogeneity and cross-disorder overlap. Premorbid functioning trajectories are thought to differ, with neurodevelopmental abnormalities associated primarily with SZ; however, the identification of empirically derived subgroups agnostic to DSM diagnosis may provide insight into pathophysiological overlap among major psychiatric disorders.

Methods: 131 patients with bipolar I or II disorder (BD; n=95) or schizophrenia or schizoaffective disorder (SZ; n=36) were assessed on premorbid adjustment, clinical symptoms and functioning. Premorbid social and academic adjustment scores were used to conduct a hierarchical cluster analysis. Mixed ANOVA examined cluster differences on trajectory patterns, symptoms, and functioning.

Results: Patients were optimally clustered into 3 groups: cluster 1 had stable good social/stable good academic (n=62; 51 BD, 11 SZ), cluster 2 had stable poor social/stable good academic (n=27; 19 BD, 8 SZ), and cluster 3 had declining intermediate social/declining poor academic (n=42; 25 BD, 17 SZ) premorbid adjustment. Cluster 1 had the most females, most education, mildest symptoms, and best social adjustment. Cluster 2 had more negative symptoms and worse social adjustment than cluster 1. Cluster 3 had more males, less education than cluster 1, more severe symptoms overall than clusters 1 and 2, more negative and depressive symptoms than cluster 1, and worse social adjustment than cluster 1.

Conclusions: Each of the three subgroups identified by premorbid adjustment profiles contained both BD and SZ patients, suggesting cross-diagnostic overlap in neurodevelopmental trajectories. These data support the use of non-DSM-based classification to identify subgroups that may share common etiologies.

Supported By: R01100125; VA Merit 1101XC000005-01

Keywords: Schizophrenia, Bipolar Disorder, premorbid adjustment, Transdiagnostic

332. Epigenetic Effects of Sex Hormones on Anxiety-Related Behaviors

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Background: Anxiety and depression are two times more prevalent in women than in men. Sex-hormone fluctuation is likely a major factor contributing to females’ increased vulnerability, although the mechanisms are poorly understood. Sex hormones induce changes in chromatin organization and dynamically regulate gene expression, which remains underexplored in the brain. Moreover, epigenetic mechanisms can contribute to anxiety-related behavior. We propose that 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 estrous cycle-dependent variations in anxiety-related behaviors.

Methods: After following the estrous cycle in mice, 20 females in diestrus (low-estrogen) phase, 20 females in proestrus (high-estrogen) phase, and 20 males were included. Animals underwent testing for anxiety-like behavior: open-field, light-dark box, elevated-plus maze. The hypothalamus and hippocampus were isolated. Gene expression was examined using qRT-PCR for Esr1/2, Dnmt1/3a, Bdnf. Neuronal chromatin organization was assessed using FACS followed by ATAC-seq.

Results: Female rodents in diestrus phase exhibit significantly higher indices of anxiety-like behavior compared to proestrus females and males. These phenotypes are associated with variation in hypothalamic gene expression, including Esr2, Bdnf, and an epigenetic regulator Dnmt1, suggesting widespread epigenetic differences among groups. Moreover, global differences in neuronal chromatin organization are observed between groups, providing novel candidate genes and pathways underlying sex differences in anxiety-related behavior.

Conclusions: Unraveling the mechanisms through which sex hormones dynamically affect brain function and behavior will increase our understanding of the brain sexual dimorphism and help tailor sex-specific approaches to treat depression and anxiety disorders.

Supported By: NARSAD Young Investigator Grant 22811; Fordham University Faculty Research Grant

Keywords: Epigenetic, Sex Hormones, chromatin, Anxiety, Sex differences

333. Sex Differences in Leukocyte Composition and Transcriptional Profiles Associated with Lifetime Post-Traumatic Stress Disorder (PTSD)

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Background: Post-traumatic stress disorder (PTSD) is a debilitating mental disorder that is precipitated by trauma exposure. Women show significantly greater risk for PTSD than men given similar levels of trauma exposure, yet sex differences have not been adequately investigated.

Methods: Adult participants (N=101) with leukocyte-derived Illumina HT-12 microarray data were drawn from the Detroit Neighborhood Health Study. Raw data were pre-processed, filtered, and batch-corrected before leukocyte composition estimation and expression analyses. Sex*PTSD interaction estimates for relative leukocyte proportions were calculated for each cell type. Transcriptional profiles for lifetime PTSD were assessed separately in each sex by differential expression analyses and gene set analyses of KEGG pathways and GO terms.
Results: Leukocyte composition analyses revealed a prominent sex*PTSD interaction with males showing an increase, and females showing a decrease in relative monocyte proportions with lifetime PTSD (p<0.05). In contrast, although degree of differential expression varied between sexes in 271 genes associated with lifetime PTSD (FDR<=0.05), the sex differences were nuanced compared to the general PTSD-associated expression profiles observed in both sexes. Likewise, most pathways dysregulated in lifetime PTSD were common to both sexes; however, degree of dysregulation in core genes differed.

Conclusions: Our study suggests that leukocyte composition, namely alterations in relative monocyte proportions, is a major sex difference associated with lifetime PTSD. Sexually dimorphic transcriptional differences associated with lifetime PTSD may be more subtle and further study of the context of dysregulation, such as cell-type specific alterations, will allow resolution of how long-term, persistent alterations associated with PTSD may be different between sexes.

Supported By: NIH grants: R01 DA022720, DA022720-S1, and RC1 MH088283; University of Illinois: CompGen Fellowship

Keywords: PTSD, Sex differences, gene expression, leukocyte, cell heterogeneity

334. Expression Levels of XIST RNA Predict PTSD and Chronic Pain Outcomes in Women Experiencing Motor Vehicle Collision

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Background: Women experiencing motor vehicle collision (MVC) are at substantially increased risk of both PTSD and chronic post-traumatic pain (CPTP). X chromosome inactivation is one candidate mechanism contributing to such differences, and the long non-coding RNA X-inactive specific transcript (XIST) is known to be a major regulator of XCI. We hypothesized that XIST levels would predict PTSD and CPTP in women experiencing MVC.

Methods: African American women age 18 to 65 presenting to the emergency department after MVC were enrolled, those who had total RNA sequencing data available (Illumina HiSeq, n=66) were included in this analysis. PTSD (IES-R) and CPTP (0-10 numeric rating scale) symptoms were assessed 6 weeks, 6 months, and 1 year after MVC. Repeated measures logistic regression, t-tests, and correlation analyses were used to evaluate relationships between transcripts and clinical outcomes.

Results: In repeated measures multivariate regression models adjusted for age, study site, and time following MVC, XIST expression levels predicted both PTSD (p=1.9x10-4) and CPTP severity (p=0.0013). For both outcomes, higher XIST RNA expression levels were associated with increased risk. In secondary analyses, 9/19 (47%) X chromosome genes previously shown to be tightly regulated by or escapees of XCI were correlated with XIST RNA expression levels (p<0.05), nine significantly predicted PTSD, and six significantly predicted CPTP (p<0.05).

Conclusions: These data suggest that XIST and related X-chromosome transcript levels predict PTSD and pain outcomes in women experiencing MVC. Further studies are needed to replicate these findings and examine potential mechanisms.

Supported By: R01 AR060852

Keywords: Sex differences, PTSD - Posttraumatic Stress Disorder, Trauma Exposure, transcription regulation, chronic pain

335. Gender Differences in the Uncinate Fasciculus in Children and Adolescents with ASD as Compared to Typically Developing Youth

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Background: Autism spectrum disorder (ASD) has been shown to affect predominantly males, with a male:female ratio reaching almost 5:1. Disconnectivity of neural networks important for social cognition is one of the major neuroanatomical correlates of ASD, although the majority of the neuroimaging studies thus far have included predominantly male participants. Thus, gender differences in connectivity in ASD have not been well characterized. The goal of our study was to evaluate integrity of a white matter tract important for social cognition (uncinate fasciculus, UF) in a more gender-balanced sample.

Methods: We conducted tractography of the UF in children and adolescents (ages 11-17) with ASD (17 girls, 11 boys) and typically developing (TD) controls (15 girls, 14 boys).

Results: Using ANOVAs with dependent variables axial diffusivity (AD), radial diffusivity (RD) or fractional anisotropy (FA) and independent variables Gender and Group (ASD vs. TD), we found significant Group effects with lower FA in ASD (as compared to TD youth) for the left and right UF (F(df)= 20.271(1,51), p<0.0005 and F(df)=30.722(1,51), p<0.0005, respectively), and increased RD in the left and right UF (F(df)=6.394(1,51), p=0.015 and F(df)=20.449(1,51), p<0.0005, respectively) in the ASD group. Furthermore, the left UF showed a significant interaction between Gender and Group (F(df)=8.626(1,51), p=0.005), such that boys with ASD had significantly lower FA as compared to both girls with ASD and TD boys (t=-2.625, p=0.015 and t=-4.706, p<0.0005, respectively).

Conclusions: These preliminary results suggest that ASD may be associated with different patterns of connectivity in boys vs. girls with ASD in a pathway important for social cognition.
336. VIP Interneuron Cholinergic Responses are Altered in Multiple Models of Autism
Margaret Cunniff and Vikaas Sohal
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Background: VIP interneurons are known to be recruited by behaviorally alert states and rewarding or aversive stimuli. VIP interneurons are also targets of the neuromodulator acetylcholine. However, the exact relationship of VIP interneurons to behavior, and possible alterations in VIP interneurons associated with disorders such as autism remain largely unknown.

Methods: We used patch clamp recording in brain slices to characterize the electrophysiological properties of VIP interneurons in the prefrontal cortex of wildtype mice and two distinct models of autism, Fragile-X knockout mice and prenatal valproate exposure. We also characterized the responses of VIP interneurons to the cholinergic agonist carbachol. VIP interneurons were bilaterally optogenetically inhibited in the mPFC during social behavior. VIP interneuron activity during social behavior was recorded using fiber photometry and calcium imaging. Statistics were done with ANOVAs.

Results: In wildtype mice, acetylcholine causes a significant increase in spike halfwidth and excitability in VIP interneurons. In both autism models, however, this increase in excitability is impaired and the increase in halfwidth is enhanced. Inhibiting VIP interneurons optogenetically during social behavior causes an increase in social interaction in wildtype mice. Recording the bulk calcium signal from VIP interneurons using fiber photometry shows VIP interneurons decrease their activity following the initiation of social interaction.

Conclusions: VIP interneurons are robustly modulated by acetylcholine, and this modulation is consistently altered in two distinct mouse models of autism. Furthermore, VIP interneurons play a major role in modulating social interaction. VIP interneurons thus may contribute to abnormal social behavior in autism and represent a novel therapeutic target.

Supported By: SFARI, NSF
Keywords: acetylcholine, Autism, interneurons, social behavior, optogenetics

337. Neuropsychiatric Profiles of Children and Adolescents with Hypothalamic Hamartomas
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Background: Hypothalamic hamartomas are rare brain malformations characterised by a clinical syndrome of seizures, central precocious puberty, behavioral, emotional and cognitive difficulties. Psychiatric symptoms often present the greatest burden of morbidity for patients and families. Due to the rarity of the disease, the heterogeneity of the presentation, and the multifactorial aetiology, prognosis is varied and management strategies are yet to be standardised.

Methods: The notes of 46 pediatric cases with hypothalamic hamartomas were examined retrospectively. Demographics, psychiatric symptoms, cognitive functioning, epileptic profiles, and pubertal status were recorded. ICD-10 codes for psychiatric disorder were assigned to applicable cases.

Results: 61% of cases were male. The mean age at diagnosis was 4.2 years (0-14 years). 71.7% of the cases met criteria for ≥ 1 ICD-10 Axis 1 psychiatric disorder. Attention Deficit Hyperactivity Disorder, Generalized Anxiety Disorder and Autism Spectrum Disorder were most frequent. 46% experienced characteristic rage attacks. 50% had some degree of intellectual disability, most commonly mild. 63% of cases experienced seizures, most commonly gelastic in nature. 40% of cases had precocious puberty.

Conclusions: This data set represents one of the largest in the pediatric hypothalamic hamartoma literature. A significant proportion of cases have psychiatric disorders and intellectual disability. These presenting features are a product of numerous aetiological factors. The direct brain-behaviour effects from disrupted hypothalamic functioning, possible epileptic encephalopathy resulting from refractory seizures and impact of antiepileptic medications are all contributory. These findings also provide insight into the pathoaeiology of other neuropsychiatric disorders where hypothalamic dysfunction has been implicated.

Keywords: hypothalamic hamartoma, seizures, aggression

338. Enabling Precision Psychiatry through ‘omics’: From Biomarkers to Biological Pathways
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Background: Schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD) are severe mental disorders regarded as syndromes and defined by a clustering spectrum of signs and symptoms. Thus far, there is no single defining clinical or pathological hallmark for any of those disorders, and their symptoms profiles overlap with each other in what is considered the schizoaffective spectrum. The lack of knowledge about their neurobiology hampers the identification of biomarkers, which could guide risk, prognosis, clinical diagnosis and therapeutic decisions.

Methods: We performed a systematic review of all studies employing proteomics or metabolomics in peripheral blood of persons with SZ, BD, or MDD compared to controls and extracted all differentially expressed proteins. After, we derived the involved biological pathways according to which altered proteins were unique to SZ, BD, or MDD and to which were shared using Ingenuity Software.
Results: These most common proteins found in SZ, BD, and MDD, were further analyzed using the Ingenuity Pathways Analysis (IPA, Ingenuity Systems), which provided a protein network of interactions. The biological pathway more consistently associated with BD was related to mitochondrial dysfunction, and with MDD and SZ was lipid metabolism. Pathways related to energy metabolism and inflammation were shared among these three disorders.

Conclusions: A fundamental research approach to the identification of novel biomarkers, which will address the underpinnings of each disorder, has been acknowledged as an absolute need. Using a system biology approach, we were able to show that biological pathways in SZ, BD, and MDD might differ.

Keywords: Biomarkers, systems biology, Bipolar Disorder, Schizophrenia, Precision Medicine

339. Biclustering of Blood Gene Expression Data Identifies Patient Subtypes with Different Biological Pathologies in Major Depressive Disorder

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Background: Major depressive disorder (MDD), as defined in the DSM 5, brings together a group of patients under one diagnosis who are heterogeneous at the level of both clinical characteristics and biology. In most biomarker studies, MDD patients as one group are compared against healthy controls. Biclustering algorithms further enable the identification de novo patient-gene clusters, breaking data into patient subgroups with distinct biology.

Methods: Microarray gene expression data was obtained from whole blood in the Janssen-BRC study (94 MDD and 100 control). We applied the SSVD and Cheng-Church biclustering algorithms, and developed a 2-D extension to Weighted Gene Coexpression Network Analysis (WGCNA). Resulting biclusters were filtered based on the separation of bicluster subjects from other MDD subjects and healthy controls using support vector machines (AUC > 0.8)

Results: Forty-one unique biclusters were selected which identified multiple gene sets and biological processes as dysregulated in different, but partly overlapping, subsets of MDD patients. The key biological drivers identified were immune processes, and RNA and energy metabolism. The RNA and energy metabolism biclusters showed significant association with BMI and body weight (Wilcoxon p < 0.0001). Immune-driven biclusters showed a weak association with depression severity (Wilcoxon p < 0.1). Differences were also seen in gender and anxiety for specific biclusters.

Conclusions: Biclustering was effective in defining robust subgroups of patients based on differential expression of genes related to specific biological pathways, which also appear to relate to clinical parameters. In the future these gene sets will be tested against antidepressant response, and patient outcomes.

Supported By: Janssen Research & Development, LLC

Keywords: Clustering, Precision Medicine, Depression, Gene Expression, Biomarkers

340. Repetitive Brain Stimulation Induces Long-Term Plasticity across Patient Populations and Spatial Scales

Corey Keller1, Wei Wu1, Rachael Wright1, Lewis Kerwin1, Kasra Sarhad1, Naho Ichikawa2, Julia Huemer3, Lisa McTeague4, and Amit Etkin1

1Stanford University, 2Hiroshima University, 3Medical University of Vienna, 4Medical University of South Carolina

Background: Transcranial magnetic stimulation (TMS) targeting the left dorsolateral prefrontal cortex (dLPFC) is a commonly-used treatment for depression. However, our understanding of the mechanism by which TMS exerts its antidepressant effect is limited.

Methods: We randomized 30 depressed patients to daily real versus sham left dLPFC rTMS (2:1 real/sham ratio), analyzed in an intent-to-treat manner with linear mixed modeling. Single pulse TMS-induced evoked potentials (TEPs) were recorded before and after treatment. Additionally, 10 healthy controls underwent a paired-pulse TEP protocol. Finally, to complement these non-invasive studies, focal repetitive electrical stimulation was applied in a rTMS-like pattern in four patients with intractable epilepsy and after-effects were quantified.

Results: We found that real rTMS was associated with a significantly greater reduction in the p60 (p < 0.05) and p200 (p = 0.002) potentials compared to sham rTMS, which localized to the left dLPFC and medial PFC. Clinical outcomes were better for those patients with larger p60/p200 TEPs at baseline (p < 0.001) or in whom there was a greater rTMS-related reduction in these TEPs (p < 0.017). The paired-pulse experiment furthermore demonstrated that the p200 potential reflects intracortical inhibition. Intracranial studies also demonstrated plasticity in electrically-evoked responses after repetitive stimulation.

Conclusions: Daily rTMS induces long-lasting neuromodulatory effects temporally and spatially removed from the site of rTMS stimulation, which are highly predictive of clinical outcome, and which appear to involve a decrease in intracortical inhibition (hence resulting in a net increase in excitability). Future applications include utilization of this TMS/EEG biomarker to optimize stimulation site, monitor efficacy, and predict treatment outcome.

Supported By: DANA foundation

Keywords: TMS-EEG, treatment-resistant depression, dLPFC

LATE BREAKING POSTER SESSION
Thursday, May 18, 2017, 5:00 PM – 7:00 PM

Late Breaking Poster Session

The Late Breaking poster abstracts were accepted after this supplement was published. See the On-Line Program Planner or Mobile App for the complete abstract.
341. Dissecting the Molecular Mechanisms of Vocal Learning and Spoken Language

Erich Jarvis

Duke University Medical Center, Durham, North Carolina

Our long-term goal is to decipher the molecular mechanisms that construct, modify, and maintain neural circuits for complex behavioral traits. One such trait is vocal learning, which is critical for song in song-learning birds and spoken-language in humans. Remarkably, although all are distantly related, song-learning birds (songbirds, parrots, and hummingbirds) and humans have convergent forebrain pathways that control the acquisition and production of learned sounds. This convergent anatomy and behavior is associated with convergent changes in multiple genes that control neural connectivity and brain development, of which some when mutated are associated with speech deficits. Non-human primates and vocal non-learning birds have limited or no such forebrain vocal pathways, but yet possess forebrain pathways for learning and production of other motor behaviors. To explain these findings, I propose a motor theory of vocal learning origin, in which brain pathways for vocal learning evolved by brain pathway duplication of an ancestral motor learning pathway. Once a vocal learning circuit is established, it functions similarly as the adjacent motor learning circuits, but with some divergences in neural connectivity. To test this hypothesis, we are attempting to genetically engineer brain circuits for vocal learning. These experiments should prove useful in elucidating basic mechanisms of speech and other complex behaviors, as well as their pathologies and repair.

References

disease. This is true of severe disorders as different as breast cancer and schizophrenia. The responsible genes are of course different, but both are guided by evolutionary processes and constraints. I will suggest how evolutionary forces generate vast genetic heterogeneity in human illness by introducing many new variants in each generation. Current sequencing technologies offer the possibility of finding rare disease-causing mutations and the genes that harbor them.

References


SYMPOSIUM
Psychobiology of Resilience: From Genes to Network Models
Friday, May 19, 2017 - 12:30 PM - 2:30 PM
Sapphire AB
Chair: Adriana Feder
Co-Chair: Robert Pietrzak

344. FKBP5 Methylation: Stable Trait or Fluctuating State?
Rachel Yehuda1, Linda M Bierer2, Janine D Flory2, Nikolaos P Daskalakis3, and Heather N Bader2

1Mount Sinai School of Medicine/JJP VA 2James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, 3Mount Sinai School of Medicine

Background: There has been great interest in understanding the relevance of FKBP5 methylation to the psychobiology of resilience. Studies will be presented that illustrate state-related as well as enduring alterations in FKBP5 methylation in the promoter region and intron 7, respectively.

Methods: Combat veterans with PTSD participated in a prolonged exposure therapy trial in which epigenetic markers were determined before and after treatment. In a second series of studies, FKBP5 methylation was studied Holocaust survivors and in adult Holocaust offspring, and compared with ethnically matched controls.

Results: Results from the psychotherapy trial demonstrate changes in FKBP5 methylation in the promoter region of the gene in association with treatment induced recovery (response x time: F(2,24)=4.58, p=0.021), suggesting that methylation in the promoter region may be a correlate of symptom improvement. Alternatively, FKBP5 methylation in the intron 7 region of the gene has been linked with genotype, childhood adversity, and more recently, intergenerational effects of trauma on offspring. Increased FKBP5 methylation at intron 7 in Holocaust survivors was associated with reductions at the same site in their offspring (r=-.44, n=33, p=.010). Moreover, an association between FKBP5 methylation in intron 7 and early age of parental exposure (F(3,77)=6.49, p=.001) was shown in an expanded series of offspring. These findings suggest the influence of developmental programming in determination of FKBP5 methylation at intron 7, and further suggest the possibility of an intergenerational protective effect.

Conclusions: These findings, and molecular mechanisms that may underlie them, will be discussed in the context of the psychobiology of resilience.

Supported By: DoD (W81XWH-06-0032), NIMH (1RC1MH088101)
Keywords: resilience, trauma, prolonged exposure, epigenetic, FKBP5

345. Hippocampal Activation and COMT Genotype Mediate the Relationship between Childhood Trauma and Resilience
Sanne van Rooij1, Jennifer Stevens2, Timothy Ely2, Negan Fan2, Alicia Smith2, Kimberly Kerley2, Adriana Lori2, Kerry Ressler3, and Tanja Jovanovic2

1Emory University School of Medicine, 2Emory University, 3McLean Hospital

Background: Most trauma survivors do not develop a psychiatric disorder, yet a better understanding of mechanisms enhancing resilience could benefit those at risk. Here we investigated genetic and imaging measures that may influence the relationship between childhood trauma and resilience.

Methods: Functional imaging data was collected in 73 highly traumatized African American women with varying levels of childhood and adult trauma, PTSD and depression symptoms. A Go/NoGo procedure in a 3T MRI scanner was used to measure response inhibition. The hippocampus was used as region of interest for the analyses. DNA from saliva was used to determine COMT genotype (Val/Val, n=38, Met carriers, N=35), as this gene has often been associated with depression and PTSD. Trail-level resilience was measured with the Connor-Davidson Resilience scale (CD-RISC).

Results: The relationship between childhood trauma and traits resilience was mediated by hippocampal activation, but only in the Val/Val group (p<0.05) and not in Met-carriers. Inhibition-related hippocampal activation correlated positively with resilience (r=0.34, p=0.007), and negatively with PTSD (r=-0.27, p=0.02) and depression (r=-0.29, p=0.01). This negative relationship with PTSD symptoms was replicated in a separate acutely traumatized group recruited in the Emergency Department, where more inhibition-related hippocampal activation one month post-trauma predicted less PTSD symptoms at three (F(1,21)=8.16, p=0.009) and six months (F(1,19)=14.66, p=0.001).
Conclusions: Increased inhibition-related hippocampal activation mediated the relationship between childhood trauma and resilience, and predicted reduced PTSD symptoms after acute trauma exposure. Hippocampal recruitment during inhibition may improve the ability to use contextual information to guide behavior, and may thereby enhance resilience in trauma-exposed individuals.

Supported By: National Institute of Mental Health (R01-MH094757 to KR, R21 MH098212 to TJ, F32-MH101976 to JS, and K01-MH101380 to NF) and Howard Hughes Medical Institute (KR)

Keywords: Resilience, Hippocampus, PTSD, COMT Val/Met, Response inhibition

346. The Network Properties of Resilience: Identification of High Dimensional Genetic & Phenotypic Interactions that Regulate the Emergence of Posttraumatic Stress & Resilience following Life Threat

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1NYU School of Medicine, 2NYU School of Medicine Child Studies Center, 3University of Minnesota

Background: Consistent evidence indicates that the majority of individuals are resilient following exposure to potentially traumatic events, even if they present with known vulnerability factors. To better understand this apparent paradox, we attempt to determine the interaction between multiple factors involved in healthy or abnormal adaptation following traumatic stress using network models to determine if these dimensions form a complex adaptive network with multiple redundant pathways to resilience, making any specific risk factor less impactful on the system overall.

Methods: Specifically, we empirically identify trajectories of resilience and post-traumatic stress using a prospective cohort of police officers followed from inception of training through 72 months of active police duty using latent growth mixture modeling. Next, we built network models including background environmental and genetic factors, endocrine and physiological functioning at rest and in response to stress challenges, as well as pre- and post-trauma exposure clinical and functional measures to determine the interplay between man risk and protective factors as they influence the development of resilience or post-traumatic stress.

Results: We demonstrate that multiple redundant pathways to resilience mitigate specific risk associated with known vulnerability factors and that significant perturbation across multiple dimensions is necessary to impact the overall network structure, ultimately preventing resilience.

Conclusions: Results help to explain why resilience is the modal outcome despite the presence of vulnerability factors that may be present in an individual.

Supported By: NIMH R01 MH056350-07

Keywords: PTSD - Posttraumatic Stress Disorder, Networks, Resilience, systems biology

347. An Integrative Psychobiological Model of Resilience in World Trade Center Responders

Adriana Feder1, Robert Pietrzak2, Olivia Diab1, Leo Cancelmo1, Rachel Yehuda3, Linda M Bierer3, Nikolaos P Daskalakis1, Andrew Ratanatharathorn1, Karestan Koenen2, and Steven M Southwick2

1Icahn School of Medicine at Mount Sinai, 2Yale University, 3James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, 4Columbia University, 5Harvard University

Background: Resilience, defined as the ability to adapt successfully in the face of trauma or severe adversity, is the modal trajectory of PTSD and related psychological symptoms in World Trade Center rescue and recovery workers, and in other trauma-affected populations. Little is known, however, about the psychobiology of resilience.

Methods: WTC responders (n=192, 83% male, mean age=55) with PTSD symptoms spanning the full dimensional spectrum were recruited from the WTC Health Program using stratified random sampling. Participants completed clinician-administered interviews, the dexamethasone suppression test (DST) and blood collection for biomarker assays an average of 13 years post-9/11/2001.

Results: Initial analyses revealed a significant main effect of the rs41423247 SNP in the glucocorticoid receptor gene (NR3C1), and interactions of this SNP and FKBP5 SNPs rs1360780 and rs9296158 with WTC-related exposures in predicting WTC-related PTSD symptoms, which persisted after adjustment for sociodemographics and childhood trauma. Protective allele homozygotes for NR3C1 rs41423247 (G/G), and FKBP5 rs1360780 (C/C) and rs9296158 (G/G) SNPs were highly resilient, with PTSD symptoms remaining sub-diagnostic even at the highest levels of WTC exposure. Further, among WTC responders with these FKBP5 genotypes, DST cortisol suppression was significantly higher in resilient than symptomatic responders, with the opposite pattern observed in risk allele carriers.

Conclusions: These initial results implicate genetic polymorphisms in NR3C1 and FKBP5 in predicting resilience in WTC responders. Further analyses will incorporate neuroendocrine, epigenetic, and gene expression variables into an integrative model of resilience that can be used to inform prevention and treatment efforts for this population.

Supported By: CDC/NIOSH U01OH010407 and U01OH010886 grants

Keywords: resilience, psychobiology, HPA axis, Genotype, World Trade Center responders

SYMPOSIUM

Neuromodulation of Brain Circuits across Treatment Modalities: Implications for Predictive Biomarkers of Treatment Resistant Depression

Friday, May 19, 2017 - 12:30PM - 2:30PM

Sapphire EF

Chair: Yvette Sheline

Co-Chair: Mark George
348. Mechanisms of TMS therapeutic Action: A Dimensional Circuit-based Approach

Erik Lee², Jared Zimmerman³, Nicolina Bruno², Skye Lewis², Kristen Ellard², Tracy Barbou², and Joan Camprodon¹

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Background: TMS is a noninvasive neuromodulation technique with approved indications for the treatment of MDD. Despite its established safety and efficacy, a weak understanding of its mechanisms of action represents an obstacle for much needed translational innovations to increase the clinical and public health impact of this intervention. In this talk, we will present data that illustrates the circuit-based mechanisms of TMS antidepressant action, and also dimensional modulation of reward processing (i.e., anhedonia and amotivation).

Methods: We recruited 16 patients with MDD who underwent TMS treatment. Patients had two identical study visits before and after the full course of treatment. Each visit included an MRI scan (high-resolution T1, resting-state fMRI, and diffusion-MRI), clinical assessments of depression (HAMD), and dimensional assessment of anhedonia and amotivation with the Temporal Experience of Pleasure Scale (TEPS). After standard data preprocessing, whole-brain connectivity analyses were conducted using subgenual cingulate cortex and nucleus accumbens seeds to understand mechanisms of (syndromal) antidepressant action and (dimensional) modulation of anhedonia and amotivation. Pearson correlations coefficients were computed between individual seed regions and all remaining whole-brain voxels. Whole brain regressions were conducted using changes in HAMD and TEPS scores.

Results: We identified changes in connectivity between our seed regions and nodes in the fronto-parietal control, salience and default networks that explained improvement in depression, anhedonia and amotivation.

Conclusions: These results highlight the circuit-level mechanism of TMS therapeutic action in patients with MDD, focusing on depression as a syndrome and anhedonia/amotivation as key clinical and behavioral dimensions.

Supported By: Harvard Mind-Brain-Behavior Faculty Grant. HMS Dupont-Warren Grant.

Keywords: TMS, Connectivity, MDD, mechanism of action

349. Neuroimaging Biomarkers of ECT Response

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Background: Electroconvulsive therapy (ECT) is one of the most effective treatments for depression, yet its mechanism of action remains unknown. To date, we are unable to predict ECT treatment response or determine the most effective treatment option for an individual patient.

Methods: We longitudinally collected resting state fMRI (rs-fMRI) in sixteen patients (48.5±13.6 yrs; 6 females) who were receiving bifrontal ECT for treatment-resistant depression. We scanned patients before the first ECT session (TP1); within 36 hours after the first ECT (TP2); and within 36 hours after the last or 8th ECT, whichever occurred first (TP3). Ten healthy comparison subjects underwent the same neuroimaging procedures. Depression was assessed with the Hamilton Depression Rating Scale (HAM-D). The primary measure derived from rs-fMRI was the fractional amplitude of low-frequency fluctuation (fALFF) and seed-based functional connectivity analysis based on our initial findings. We compared treatment-related changes in HAM-D scores to pre- and post-treatment fALFF and connectivity measures.

Results: Patients’ mood improved significantly with ECT treatment (HAM-D % change: 63.9 ± 16.6 %, p<0.001). We found a significant decrease in fALFF in the subcallosal cingulate cortex (SCC). fALFF in the SCC region was significantly higher at baseline in depressed patients versus HC (p=0.002); the change in fALFF was significantly correlated with the antidepressant efficacy of ECT (r=0.52, p=0.04).

Conclusions: These results suggest that the antidepressant effect of ECT may be mediated by down-regulation of SCC activity and connectivity. SCC function may serve as an important biomarker of target engagement in the development of novel therapies for TRD.

Keywords: Resting state fMRI, Electroconvulsive therapy, Neuromodulation, Subgenual anterior cingulate cortex, Treatment Resistant Depression


Yvette Sheline¹, Haochang Shou², Zhen Yang², Desmond Oathes³, Theodore Satterthwaite³, Phillip Cook², Emma Satchell², and Russell Shinohara²

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Background: We investigated resting fMRI data to understand, within the same sample, the brain indices of dimensional fronto-parietal network (FPN) abnormalities across diagnostic categories (MDD and PTSD combined) and these abnormalities were then examined longitudinally following CBT treatment.

Methods: From an initial sample of 62 patients in a 12 week manualized CBT treatment protocol there were 36 completers (n = 17 MDD; 19 PTSD) and 18 comparison subjects (HC). All patients met DSM-IV-TR criteria for MDD or PTSD, respectively. All participants received an MRI scan (Siemens 3T) at baseline and 12 weeks to assess resting state functional connectivity. Only data from participants with complete data at both timepoints was included. Longitudinal functional principal components analysis (LFPFC) was performed on functional connectivity of the amygdala with the FPN.
Results: LFPFC identified four principal components (PCs) that contributed significantly to the longitudinal change in connectivity with amygdala across patients. The second PC differentiated CBT-treated patients in having significantly increased connectivity of the amygdala with the FPN following CBT (p = 0.01) compared with HC, who did not change. A post-hoc voxel-wise ROI analysis confirmed changes in regions within the FPN (e.g., inferior frontal gyrus) in patients following CBT (p=0.04), whereas in HC, connectivity did not change (p=0.2).

Conclusions: We found evidence for the hypothesis that CBT treatment is associated with changes in connectivity between the amygdala and the FPN. CBT may work by strengthening connections with brain regions involved in cognitive control, thus correcting cognitive distortions common to both MDD and PTSD.

Supported By: RC MH089704 (YIS), R01MH064821 (YIS), K24MH098260 (YIS); R01MH107703 (TDS) K23MH098130 (TDS); K23 MH090366 (SEB)

Keywords: Major Depressive Disorder (MDD), PTSD - Posttraumatic Stress Disorder, Dimensional, Constrained Principal Component Analysis

351. Early and Late Cerebral Blood Flow Effects of Subcallosal Cingulate DBS for Depression: Emerging Evidence of Stimulation Induced Plasticity

Helen Mayberg1, Callie McGrath2, Justin Rajendra2, Kisueng Choi2, Patricio Riva Posse2, Andrea Crowell2, and Paul Holtzheimer3

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Background: Behavioral effects of subcallosal cingulate DBS for depression occur in two stages: a rapid change in interoceptive/exteroceptive awareness with first stimulation at the optimal target, and a slower progressive improvement in global symptoms over weeks-months with chronic stimulation (1). Longitudinal cerebral blood flow (CBF) and electrophysiological monitoring allows characterization of this chronology.

Methods: Seventeen patients with TRD underwent SCC DBS (2). CBF was measured using positron emission tomography (Siemens HRRT, 20 mCi 15O-H2O dose/scan x 4/session) at 4 time points: pre-implantation baseline, 1-month post-op prior to DBS, 1 and 6 months of chronic DBS. Whole brain analyses were performed to define the differential trajectory of regional CBF changes with chronic stimulation (1-way rm-ANOVA). Results were anatomically constrained to regions structurally connected to the SCC defined using tractography (3).

Results: Regional CBF changes followed 3 temporal patterns. Pattern 1: maximal changes 1 month after implantation and maintained with chronic stim: bilat SCC, MCC, R-ant insula (all decreases). Pattern 2: no post-implant effects, but changes with active stimulation: L-thalamus, hypothalamus (decreases), L-prefrontal, posterior cingulate (increases). Pattern 3: transient changes with stimulation that returned to baseline at 6 months: R-prefrontal (decreases).

Conclusions: The trajectory of CBF changes with DBS is not linear, consistent with the chronology of behavioral effects. A process of ongoing adaptation and remodeling of a predefined ‘depression network’ is posited as a contributing mechanism of action.


Supported By: Dana Foundation, Stanley Medical Research Foundation, Hope for Depression Research Foundation, Woodruff Fund. Devices donated by St Jude Medical, Inc.

Registration: FDA IDE G060028 (HSM); Clinicaltrials.gov #NCT00367003 (HSM)

Keywords: Deep Brain Stimulation, Treatment Resistant Depression, PET imaging

352. Negative Symptom Trials: Recent Results and Challenges

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UCLA & VA Greater Los Angeles

Background: Although a number of recent trials have focused on pharmacological and non-pharmacological interventions for improving negative symptoms, this area remains an unmet therapeutic need. This presentation will use data from recent studies to clarify the methodological challenges that should be addressed if effective treatments can be identified.

Methods: The results of expert consensus guidelines for negative symptom trials will be presented. In addition, data from recent positive and negative Phase 2 and Phase 3 trials of medications for negative symptoms will be critically discussed. Other data will include post hoc analysis of studies including the NIMH CATIE and the NewMeds data base to illustrate the challenges in identifying the populations that should be included in negative symptom trials.

Results: A review of available data indicates that (1) overly restrictive entry criteria for trials can lead to samples that do not reflect community populations; (2) allowing patients with moderate positive symptoms does not undermine a trials ability to find an effect on negative symptoms; (3) trials should address the large placebo effects which make it difficult to identify drug effects; (4) trials with very large numbers of sites are more likely to fail; and (4) newer negative symptom rating instruments are more likely to identify changes in core negative symptoms.
Conclusions: The availability of data from large trials of interventions for negative symptoms can be used to improve the design of future trials.

Keywords: Schizophrenia, Negative Symptoms

353. New Negative Symptom Assessment Tools for Clinical Trials
William Horan1, Felice Reddy2, and Michael Green2
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Background: There has been a recent surge of interest in developing novel treatments for the debilitating negative symptoms of schizophrenia. In this context, considerable attention has focused on developing new assessment tools for clinical trials that are grounded in contemporary clinical and affective neuroscience research, including interview- and performance-based approaches.

Methods: The psychometric properties and validity of two new interviews, the Clinical Assessment Interview for Negative Symptoms (CAINS) and the Brief Negative Symptom Interview (BNSS), have been examined in several studies. To address potential challenges associated with interview-based assessment, our team has also evaluated the suitability of conceptually related measures of reward processing for use in clinical trials in 130 outpatients and 70 healthy controls.

Results: The CAINS and BNSS both assess the primary experiential and expression-related subdomains of negative symptoms. Their psychometric properties (e.g., r’s > .40 between CAINS and community functioning) are generally comparable and strong, though their specific content and rating approaches differ. We have found that some effort-based decision making, probabilistic reward learning, and delay discounting measures show promising characteristics (e.g., large patient-control differences, test-retest correlations > .70) for clinical trial endpoints. However, these performance measures show generally small, non-significant relations to interview measures.

Conclusions: A new generation of clinical interview-based measures is now in widespread use internationally. We find generally small relations between interview and performance measures, and the research literature in this area is remarkably mixed. The inconsistent convergence between these approaches raises fundamental questions about the optimal assessment of negative symptoms.

Supported By: RO1; VA Merit
Keywords: Schizophrenia, Negative Symptoms, reward processing

354. Negative Symptoms and Cognitive Deficits Predict Different Elements of Everyday Functioning in People with Schizophrenia
Philip Harvey

University of Miami

Background: The overlap between negative symptoms and cognitive deficits is unclear: some definitions of negative symptoms include cognitive or functional deficits as features. Studies of the relationship between negative and cognitive symptoms and impairments in everyday outcomes often lack precision. We address this issue in a large sample of people with schizophrenia examined with common assessments. We hypothesized that negative symptoms would predict social outcomes, but not other outcomes and that cognition would not predict social functioning.

Methods: Patients with schizophrenia (n=1035) participated in this study. They were rated by clinician informants for their everyday functioning, tested with assessments of cognition and functional capacity, and examined with the PANSS. We tested the hypotheses with confirmatory factor analysis, using a comparison model that specified that negative symptoms, cognition, and functional capacity had equivalent influences on all aspects of outcome. In testing the hypothetical model, we fixed the correlations between negative symptoms and vocational and everyday activities to 0, similarly fixing the correlation between cognition and social outcomes to 0.

Results: The overall model had a suitable fit: RMSEA = .049, CFI = .962. Using sequential chi-square subtraction, the difference in model fit between the hypothetical and comparison models was statistically significant: Chi-square =48.8, p=.0001, indicating that the hypothetical model had a significantly better fit.

Conclusions: Our analyses supported the idea that negative and cognitive symptoms had different correlations with different aspects of functional outcomes. These data support separate treatments for negative symptoms and cognition to improve functional outcomes in people with schizophrenia.

Supported By: NIMH RO1 63116; 78775; 93432
Keywords: Negative Symptoms, Neurocognition, functional capacity, Everyday functioning

Michael Davidson

Self-Employed

Background: To compare the efficacy, safety, and tolerability of MIN-101, a compound with affinities for sigma 2 and 5-HT2A receptors, to placebo in treating negative symptoms, in patients with stable symptoms of schizophrenia.

Methods: This trial enrolled 244 patients with schizophrenia who were symptomatically stable for ≥ 3 months prior to entering the trial and had baseline scores ≥ 20 on the 3-factors negative subscale of the PANSS. Patients were randomized to daily monotherapy with MIN 101 32 mg, MIN-101 64 mg, or placebo in a 1:1:1 ratio. The primary endpoint was the PANSS negative symptom score based on the 5-factors (pentagonal) model.

Results: Statistically significant and dose dependent reduction in the primary endpoint score was demonstrated for MIN-101 32 mg and 64 mg compared to placebo (p ≤ 0.022; effect size (ES) 0.45 .and ≤ 0.003; ES 0.58, respectively). The validity of effects on the primary endpoint was supported by similar effects on most of the secondary measurements including: PANSS 3-factors negative symptoms subscale, PANSS total...
score, CGI, CDSS, and PSP. There were no statistically significant differences in PANSS positive subscale scores between MIN 101 and placebo. No weight gain or clinically significant changes in vital signs, prolactin levels, routine laboratory values, metabolic indices and extrapyramidal symptom scores (EPS) were observed.

Conclusions: Since positive symptoms and EPS did not change, the improvement in negative symptoms was not secondary to improvement in positive symptoms or EPS. MIN-101 might be the first specific treatment to have a direct effect on negative symptoms.

Supported By: Minerva Neuroscience
Keywords: Schizophrenia, negative symptoms

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**SYMPOSIUM**

**Understanding, Predicting, and Preventing Suicidality**
Friday, May 19, 2017 - 12:30 PM - 2:30 PM
Sapphire MN
Chair: Alexander Niculescu

356. Precision Medicine for Suicidality: From Universality to Subtypes and Individualization

**Alexander Niculescu**
Indiana University School of Medicine

**Background:** Suicide remains a clear, present, and increasing public health problem, despite being a potentially preventable tragedy. Its incidence is particularly high in people with overt or un(der)diagnosed psychiatric disorders. Objective identification of individuals at risk, ways of monitoring response to treatments, and novel preventive therapeutics need to be discovered, employed, and widely deployed. Previous work by our group, conducted separately in men and in women, has identified promising blood gene expression biomarkers and phenotypic measures that can predict suicidality in independent cohorts, showing some gender similarities as well as differences.

**Methods:** We investigated whether blood gene expression biomarkers can be identified that are more universal in nature, working across psychiatric diagnoses and genders. We also examined whether subtypes of suicidality can be identified based on mental state at the time of high suicidal ideation. Finally, we studied a more traditional individualized approach, by psychiatric diagnosis and gender. We then compared the universal approach to the subtypes approach and the individualized approach.

**Results:** We were successful in identifying universal biomarkers for suicidality, and show that the subtype and individualized approaches permit enhanced precision of predictions for different biomarkers. The biomarkers identified provide a window towards the biology of suicide. A series of them are targets of existing drugs used to treat mood disorders and suicidality, providing a means towards pharmacogenomics stratification of patients. Finally, bioinformatics drug repurposing analyses with the top biomarkers identified new potential therapeutics for suicidality.

**Conclusions:** We believe this work is a major step forward towards understanding, predicting, and treating suicidality.

**Supported By:** NIH Directors’ New Innovator Award (1DP2OD007363) and a VA Merit Award (2I01CX000139) to ABN.

**Keywords:** Biomarkers, Suicide, Precision Medicine

357. Stress Vulnerability and Epigenetic Variation of a Suicide Biomarker Gene, Molecular Regulation and Neuroimaging Consequences of SKA2

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¹Johns Hopkins University School of Medicine, ²Johns Hopkins Bloomberg School of Public Health, ³Max Planck Institute of Psychiatry, ⁴Rigshospitale

**Background:** We previously reported on suicide associated SKA2 DNA methylation at rs7208505 in multiple brain and blood cohorts that can act as a promising biomarker for suicide. Our data support a mechanism of risk whereby SKA2 reduces the ability to suppress cortisol following stress. Our ongoing objectives are to understand the functional regulation of SKA2 and to assess its association with neuroimaging outcomes.

**Methods:** A range of cell culture experiments including chromatin conformation capture (3C), siRNA mediated SKA2 knock down, and drug treatment were performed to assess SKA2 regulation. Targeted SKA2 pyrosequencing was performed in women with mood disorder undergoing resting state functional connectivity (rs-fc) fMRI imaging and again in a separate cohort of healthy control women undergoing [11C] DASB-PET imaging to assess synaptic serotonin levels.

**Results:** 3C experiments confirmed an interaction between 3’UTR rs7208505 DNA methylation and the SKA2 promoter, while SKA2 knock down disrupted glucocorticoid receptor mediated signaling. Treatment of HEK293 cells with fenofibrate upregulated PPAR signaling and increased SKA2 expression. SKA2 DNA methylation correlated with cortisol awakening response in N=21 healthy controls. Baseline SKA2 methylation interacted with total daily cortisol to associate with frontal cortical synaptic serotonin levels. DNA methylation in SKA2 in women with mood disorder was correlated with rs-fc variation between the both the superior frontal gyrus and posterior cingulate cortex to the amygdala in the postpartum period.

**Conclusions:** The data suggest that SKA2 variation mediates glucocorticoid signaling and downstream neuroimaging consequences and supports a mechanism of HPA axis dysregulation conferring vulnerability to suicidal behaviors.

**Keywords:** Suicide, HPA axis, SKA2, Serotonin, Epigenetics
358. Stress Response and Polyamines in Depression and Suicide

P. Adolfo Sequeira

University of California Irvine

**Background:** Despite the development of new pharmacological interventions for depression, suicide rates have increased significantly in the past 30 years. Extensive post-mortem and clinical studies have underlined the involvement of the polyamine system in depression and suicide. Polyamines play a central role in the homeostatic response to stress and we propose, are also involved in depression and suicide.

**Methods:** We have explored patterns of gene expression in suicide and non-suicide depressed brains versus controls using the NanoString platform. We also evaluated stress response, between baseline and after cortisol administration, in lymphoblastoid cell lines from controls and depressed patients with and without severe suicidal behaviors. Genes in the polyamine system and target genes modulated by polyamines or involved in stress response were investigated.

**Results:** We observed gene expression signatures associated with depression and with suicide specifically depending on the brain region explored. A decrease in gene expression of SAT1 in combination with an increase in ODC1 and AMD1 was observed in depressed suicides in the frontal cortex, anterior cingulate and hippocampus. This was accompanied in suicide victims, by an overall increase in GRIN2B gene expression, an NMDA receptor subunit particularly sensitive to polyamines. In the cell lines, the glucocorticoid receptor (NR3C1) and ODC1 showed an altered stress response in depressed patients with suicidal behaviors.

**Conclusions:** Our results show region specific polyamine gene alterations involved in both depression and suicide specifically. In conclusion, our results strongly suggest that stress in combination with polyamines play a significant role in the pathophysiology of depression and suicide.

**Supported By:** RO1 MH098554 from NIMH

**Keywords:** Cytokine, Toll-like Receptors, Post-mortem brain, Depression, Suicide

359. Is Inflammation Associated with Suicide Brain?

Ghanshyam Pandey

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**Background:** Abnormal immune function has been implicated in the pathophysiology of depression and suicide. In order to further examine the immune function in suicide we have determined pro- and anti-inflammatory cytokines and TLRs in the postmortem brain of suicide victims and control subjects.

**Methods:** We determined protein and mRNA levels of inflammatory cytokines, their membrane-bound receptors, and TLRs in the prefrontal cortex (PFC) of 24 depressed suicide victims and 24 normal control subjects. The postmortem brain samples were obtained from the Maryland Brain Collection. The subjects were diagnosed according to DSM-IV (SCID). Protein levels were determined either by ELISA or by the Western blot, and mRNA levels were determined by real time PCR (qPCR).

**Results:** We found that the protein and mRNA levels of IL-1β, IL-6, TNF-α, and LTA were significantly increased, and those of IL-10 significantly decreased in the PFC of depressed suicide victims, with no significant differences in the levels of IL-8, IL-13. Protein levels of membrane-bound receptors, such as IL-1R1, IL-1R2, IL-1RA, TNFR1, TNFR2 and Gp130, but not IL-6R, were significantly decreased in the PFC of depressed suicide victims. Protein and mRNA levels of TLR2, TLR3, TLR4, TLR6, TLR7, and TLR10 were significantly increased in the PFC of depressed suicide victims, with no significant difference in TLR5, TLR8 and TLR9.

**Conclusions:** This study shows abnormalities of adaptive and innate immunity in suicide brain as evidenced by increased protein and mRNA levels of proinflammatory cytokines, decreased anti-inflammatory cytokines and increased levels of specific TLRs in the PFC of suicide victims.

**Supported By:** RO1 MH097082

**Keywords:** Suicide, Major Depression, Stress, Polyamines

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360. Cognitive and Neuropsychiatric Screening for Early Dementia Detection

Zahinoor Ismail

Hotchkiss Brain Institute, University of Calgary

**Background:** Cognitive decline and functional impairment are the hallmarks of dementia. Emerging research describes the importance of neuropsychiatric symptoms (NPS) in dementia presentations. NPS may present in advance of cognitive impairment heralding cognitive decline. Mild Behavioral Impairment (MBI) is a new construct that operationalizes the assessment of later life onset of sustained and impactful NPS as an at-risk state for cognitive decline and dementia, with recently published research diagnostic criteria and an instrument to measure MBI, the MBI checklist.

**Methods:** We will review cognitive and neuropsychiatric screening instruments, useful in general psychiatry. We will explore the MBI checklist, and imaging and biomarkers associated with NPS that precede dementia. We will focus on the MBI domains of apathy, emotional dysregulation, irritability/agitation, social disinhibition, and psychosis.

**Results:** We will present the MBI checklist and imaging and biomarker studies designed to assess NPS as predictors of cognitive decline and dementia.

**Conclusions:** We will discuss future directions in neuropsychiatry, bridging psychiatric symptoms and neurodegenerative disease risk.
361. Dorsolateral Prefrontal Cortex Neuroplasticity Deficits in Alzheimer’s Disease
Sanjeev Kumar, Reza Zomorodi, Zaid Ghazala, Daniel Blumberger, Corinne Fischer, Zafiris Daskalakis, Benoit Mulsant, Bruce Pollock, and Tarek Rajji

Center for Addiction and Mental Health, University of Toronto

Background: Dorsolateral prefrontal cortex (DLPFC) dysfunction is well known across different stages of Alzheimer’s disease (AD). Impaired synaptic neuroplasticity is thought to be responsible for the DLPFC dysfunction. Early studies using Transcranial Magnetic Stimulation (TMS) paradigms such as ‘Paired Associative Stimulation’ (PAS), have shown motor cortex neuroplasticity deficits in AD. Neuroplasticity in DLPFC of patients with AD have not been studied so far. In this study we used PAS combined with EEG to assess DLPFC neuroplasticity in AD.

Methods: Patients with AD and healthy adults 65 years or older were enrolled. PAS (inter stimulus interval 25 millisecond) was used to induce neuroplasticity. Cortical evoked activity (CEA) was recorded using TMS- EEG. Ratio of post PAS/pre PAS CEA was used as a measure of neuroplasticity.

Results: Eighteen healthy older adults (female = 10, mean Age = 75.6, SD = 5.5) and 33 patients with AD (female = 17, mean Age = 76.5, SD = 6.2) were enrolled. Patients with AD had a lower MMSE score (mean = 22.6, SD = 3.2) as compared to healthy older adults (mean = 29.2, SD = 0.8) (p < 0.001). Further, patients with AD had impaired DLPFC neuroplasticity (mean = 1.18, SD = 0.25) as compared to healthy older adults (mean = 1.41, SD = 0.34) (Cohen’s d = 0.77, p = 0.01).

Conclusions: This is the first study showing impaired DLPFC neuroplasticity in patients with AD. These findings could lead to development of novel bio-markers and in developing targeted treatment interventions for AD.

Supported By: The W. Garfield Weston Foundation

Keywords: Neuroplasticity, TMS-EEG, Alzheimer’s Disease, cognition, Dementia

362. Role of Brain Imaging in the Diagnosis and Therapeutics of Neurocognitive Disorders
Amer Burhan

University of Western Ontario Faculty of Medicine

Background: The field of brain imaging research in neurocognitive disorders is in rapid flux. Significant investment like the Alzheimer Disease Neuroimaging Initiative (ADNI) resulted in tangible progress towards clinical utility of structural and functional brain imaging in Alzheimer’s disease and related disorders. Current published guidelines from several groups support the clinical use of some but not all of brain imaging modalities in neurocognitive disorders. Some emerging modalities are considered promising as bio markers for neurocognitive disorders but require further validation. There is an ongoing need to review and update the evidence from brain imaging research to establish clinical and research utility in neurocognitive disorders.

Methods: The author participated in the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4) held in Montreal in 2012. A focused review of the English language literature using pubmed database with relevant search terms was conducted by experts for different brain imaging modalities in neurocognitive disorders. Evidence-informed recommendations were presented and voted on by CCCDT4 participants to reach consensus.

Results: Some neuroimaging modalities were recommended for clinical use under specific circumstances and some were considered as promising emerging research tools that require further validation. Detailed of the recommendations and rationale together with updated literature summary will be presented and discussed.

Conclusions: It is important for clinicians and scientists to stay up to date with this rapidly evolving field, especially that current therapeutic disease modifying trials have integrated brain imaging to allow specific outcome measures related to the underlying pathology.

Supported By: Fourth Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD4)

Keywords: Alzheimer’s Disease, Brain Imaging, MRI, PET, Dementia

363. Theta-Gamma Coupling and Working Memory in Alzheimer’s Dementia and Mild Cognitive Impairment
Tarek Rajji

University of Toronto

Background: The prefrontal cortex is thought to support compensatory mechanisms that delay the development of Alzheimer’s dementia (AD), especially in individuals with Mild Cognitive Impairment (MCI). Working memory is supported by the prefrontal cortex and the modulation of neuronal gamma by theta oscillations (theta-gamma coupling). Combining electroencephalography (EEG) with a working memory task we assessed theta-gamma coupling during N-back performance as a potential marker of prefrontal cortical function in AD, MCI and Healthy Control (HC) participants.

Methods: Older HC (N = 20 Mean Age = 74.6, SD = 5.2; Female = 12 (60.0%)), AD (N = 26; Mean Age = 77.2, SD = 6.3; Female = 13 (50.0%)), and MCI participants N = 30; Mean Age = 70.9, SD = 6.7; Female = 14 (46.7%) . Comparisons among the three groups on 2-back accuracy and reaction time, and on theta-gamma coupling during 2-back performance were conducted. Associations were then assessed between theta-gamma coupling and accuracy or reaction time.

Results: There was a significant group effect on accuracy (F(2,52) = 13.78, p < 0.001) and theta-gamma coupling (F(2,67) = 11.5, p < 0.001) with AD participants being significantly impaired compared to MCI and HC participants.
Across the three groups, high theta-gamma coupling was associated with high accuracy and short reaction time after controlling for age, sex, and education.

**Conclusions:** Our findings suggest that theta-gamma coupling during N-back performance is a neurophysiologic mechanism of prefrontal cortical function that could serve in the future as a target for a novel intervention that will aim at preventing AD.

**Supported By:** Brain Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, Ontario Ministry of Research, Innovation and Science

**Keywords:** Alzheimer’s Disease, Mild cognitive impairment, Electroencephalography, Working memory, Theta-Gamma Coupling

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**SYMPOSIUM**

**New Perspectives on the Fear-Circuitry Model of Post-Traumatic Stress Disorder**

Friday, May 19, 2017 - 12:30 PM - 2:30 PM
Sapphire 410 AB
Chair: Belinda Liddell

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**364. The BDNF Val66Met Polymorphism Moderates the Relationship between PTSD and Fear Extinction Learning**

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^1^University of Tasmania, ^2^University of Sydney, ^3^University of New South Wales

**Background:** The low expression Met allele of the BDNF Val66Met polymorphism is associated with impaired fear extinction in healthy controls, and poorer response to exposure therapy in patients with Posttraumatic Stress Disorder (PTSD). To date, no studies have examined the relationship between BDNF genotype and fear extinction learning in PTSD.

**Methods:** One hundred and six participants (22 with PTSD, 42 trauma-exposed controls and 38 non-trauma exposed controls) completed a differential fear conditioning and extinction task and saliva samples were taken for DNA extraction and genotyped for the BDNF Val66Met polymorphism. Moderation analyses using PROCESS examined whether BDNF genotype (Val-Val vs Met carriers) moderated the relationship between group status (PTSD vs Controls) and average skin conductance response (SCR) amplitude during fear extinction.

**Results:** The PTSD group displayed significantly slower fear extinction learning compared to trauma-exposed and non-trauma exposed controls in the early extinction phase. The BDNF Val66Met polymorphism moderated the relationship between PTSD status (vs controls) and fear extinction learning, such that greater SCR amplitude during fear extinction was associated with PTSD status in individuals with the low-expression Met allele, but no relationship was demonstrated in individuals with the Val-Val allele.

**Conclusions:** This study reveals that impaired fear extinction learning is uniquely associated with PTSD in carriers of the low-expression BDNF Met allele and importantly not in those with the Val allele. This provides for the first time evidence of a direct link between reduced levels of BDNF and impaired fear extinction learning in PTSD, which may result in poorer response to exposure therapy.

**Supported By:** NHMRC

**Keywords:** PTSD - Posttraumatic Stress Disorder, Brain Derived Neurotrophic Factor, Fear Extinction

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**365. Neural Correlates of Heart Rate Variability in PTSD during Sub- and Supraliminal Processing of Trauma-related Cues**

Daniela Rabellino^1^, Wendy D’Andrea^2^, Greg Siegle^3^, Paul Frewen^1^, Reese Minshew^2^, Maria Densmore^3^, Richard W.J. Neufeld^1^, Jean Theberge^3^, and Ruth Lanius^1^

^1^Western University of Canada, ^2^The New School for Social Research, ^3^University of Pittsburgh School of Medicine

**Background:** Posttraumatic stress disorder (PTSD) is characterized by dysregulated arousal that is associated with altered cardiac autonomic response evidenced by decreased high-frequency heart rate variability (HF-HRV), an indirect measure of parasympathetic modulation of the heart. Examining the neural correlates underlying altered parasympathetic responses in PTSD is critical to understanding PTSD symptomatology during supraliminal and subliminal exposure to trauma-related stimuli.

**Methods:** We compared the BOLD fMRI response associated with HF-HRV between a PTSD group (n=18) and a healthy control group (n=17) during sub- and supraliminal processing of personalized trauma-related cues.

**Results:** In comparison to controls, the PTSD group showed decreased HF-HRV reactivity in response to both sub- and supraliminal cues. During subliminal processing of trauma-related vs. neutral words, as compared to controls, the PTSD group showed a decreased neural response associated with HF-HRV within the left dorsal anterior insula and the posterior cingulate cortex. By contrast, as compared to controls, the PTSD group showed decreased neural activity associated with HF-HRV within the posterior insula/superior temporal cortex and increased neural activity associated with HF-HRV within the left centromedial amygdala and the subgenual cingulate cortex during supraliminal processing of trauma-related vs. neutral words.

**Conclusions:** Cortical and subcortical areas crucial to the central autonomic network were associated with compromised parasympathetic modulation of autonomic arousal in PTSD. Remarkably, the contribution of both supraliminal and subliminal trauma-related stimuli to dysregulated arousal points clearly to their key role in the maintenance of hyperarousal symptoms in PTSD.

**Supported By:** Canadian Institutes of Health Research

**Keywords:** PTSD - Posttraumatic Stress Disorder, Functional MRI, Heart rate variability
366. Hippocampal-Dependent Pattern Separation and Completion of Complex Contextual Scenes

Israel Liberzon, Elizabeth Duval, and Sonalee Joshi

University of Michigan

**Background:** We have proposed that deficit in contextual processing constitute core deficits in PTSD, linking them to altered function of hippocampal-prefrontal circuits. Pattern Separation (PS) and Pattern Completion (PC) are hippocampal processes essential for contextual encoding and retrieval, but they been assessed to date using item/object identification tasks. We sought to develop a novel fMRI task to assess PS and PC processes using complex scenes that probe hippocampal engagement.

**Methods:** Subjects completed two PS and PC tasks in fMRI: the established Mnemonic Similarities Task that presents images of common objects during encoding and recall phases, distractors and lures, and a novel Context Separation and Completion Task (CSC), that uses degraded/ altered images of previously learned scenes. Participants indicate which scene they are seeing, or whether they are seeing a new scene, to assess PS and PC of complex scenes.

**Results:** Preliminary findings (p < .01, uncorrected; data collection ongoing) demonstrate hippocampal activation during the MST, and during both encoding (30, -19, -14) and recall phases (24, -26, -10; all trials > implicit baseline). The new CSC task produced similar results, with hippocampal activation during PC (-30, -4, -20).

**Conclusions:** Though preliminary, our results replicate hippocampal activity associated with PS and PC, and extend these findings to a task examining PS and PC using altered/degraded complex scenes that can be used as contextual information in the next stage of this study. We will test hippocampal dependent memory deficits that may underlie fear learning abnormalities in PTSD.

**Keywords:** context, Pattern Separation, Hippocampus, PTSD

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367. Neural Correlates of Threat Reactivity and PTSD Symptoms in Refugees with Torture Trauma

Belinda Liddell1, Jessica Cheung1, Miriam Den1, Kim Felmingham2, Gin Malhi3, Pritha Das3, Angela Nickerson1, Mirjana Askovic4, Jorge Aroche4, Mariano Coello4, and Richard Bryant1

1UNSW Australia, 2University of Melbourne, 3University of Sydney, 4NSW Service for the Treatment and Rehabilitation of Torture and Trauma Survivors (STARTTS)

**Background:** It is estimated that one in five refugees are torture survivors, with torture being the single biggest predictor of posttraumatic stress disorder. Torture can have significant long-term ramifications on the psychological health of survivors, but the effects on the brain are less clear.

**Methods:** In this study, 80 refugees including 30 torture survivors, completed a threat-related perception task (fear faces), whilst undergoing fMRI scanning. Multiple regression analyses were conducted to determine group differences in fear processing as a function of torture exposure, in interaction with PTSD and dissociative symptoms, torture severity and overall trauma dosage.

**Results:** Torture severity and trauma load corresponded to increased engagement of the medial prefrontal cortex to fear faces amongst torture survivors (p < .05, family-wise error corrected). Avoidance symptoms were correlated with activity in the left anterior insula, and emotional numbing symptoms were associated with increased activity in bilateral hippocampus in torture survivors. Conversely for arousal symptoms, non-torture survivors evidenced stronger activity in bilateral hippocampus. Re-experiencing and dissociative symptoms did not correlate with group differences. After controlling for all symptoms and trauma, torture survivors significantly engaged the right amygdala.

**Conclusions:** The results suggest that torture trauma has a significant impact on fear processing substrates in the brain, irrespective of PTSD symptoms. MPFC activity to fear cues corresponded to the level of torture severity, consistent with an ‘over-modulation of emotion’ neural model. However, torture survivors also evidenced heightened threat detection after controlling for symptoms and trauma exposure. The findings suggest that fear circuits are impacted in important ways by torture exposure.

**Supported By:** Australian Research Council

**Keywords:** refugee, torture, PTSD Symptom Severity, fear neurocircuitry, fMRI

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368. Deep Dynamic Phenotyping: Neural Changes Underlying Fluctuations in Bipolar Disorder Over One Year

Justin Baker1, Nora Mueller2, Jukka Pekka Onnela3, Dost Ongur4, and Randy Buckner5

1McLean Hospital/Harvard University, 2McLean Hospital, 3Harvard School of Public Health, 4McLean Hospital/ Harvard Medical School, 5Harvard University

**Background:** Longitudinal studies of biological changes in individuals with bipolar disorder are essential to advance our understanding of this inherently unstable condition. Here we compared behavioral and brain anatomic changes over one year in individuals with active mental illness, which until recently was not feasible due to the high costs of scanning and the lack of low-burden behavioral phenotyping strategies.

**Methods:** Each participant received a daily symptom questionnaire and audio survey via a smartphone app, which also passively collected sensor data (e.g., accelerometer, GPS, power state, SMS/calls). Serial brain MRI, including T1 and BOLD fMRI (using tasks and rest periods), were obtained from each participant every 3-4 weeks along with continuous wrist
actigraphy (Philips Actiwatch2). General Estimating Equations (GEE) were used to estimate relationships between measures, and evidence for neural changes in a priori defined brain systems was examined in relation to objective and subjective illness measures.

**Results:** To date, five participants with psychotic illness have been followed for >250 days each using continuous smartphone tracking and up to 10 MRI measurements to examine variance in MRI measures in relation to both conventional and objectively defined surrogates of illness activity, yielding many previously unknown relationships and establishing the feasibility of this approach.

**Conclusions:** These studies demonstrate proof-of-concept for applying a deep dynamic phenotyping approach in individuals with severe mental illness, suggesting a new powerful paradigm for evaluating which behavioral and pharmacological interventions lead to causal changes in brain structure, brain function, and ultimately behavior.

**Supported By:** Anonymous Donor

**Keywords:** Longitudinal Brain Imaging, digital health, pervasive sensing, Severe Mental Illness, Bipolar Disorder

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369. Digital Phenotyping in Schizophrenia

**John Torous**¹, Jukka Pekka Onnela², Patrick Staples², Luis Sandoval¹, Ian Barnett², and Matcheri Keshavan¹

¹Harvard Medical School, ²Harvard School of Public Health

**Background:** The purpose of our study is to determine if self reported symptom surveys and passive data (GPS, accelerometer, voice samples, call logs, and text logs) collected from patients with schizophrenia in real time on their personal smartphone may be useful in predicting relapse.

**Methods:** Research subjects are adults (age 18-45, both sexes) who have been diagnosed with schizophrenia or schizoaffective disorder and are currently in treatment. Inclusion criteria include owning a smartphone capable of running the study application, Beiwe, developed by the Onnela Lab at the Harvard School of Public Health. Subjects use the smartphone app for a three-month period. During this period the app constantly collects data, up to one million data points per day per subject as outlined in the background section.

**Results:** To date 14 of 20 subjects have been recruited into the study. No subjects have complained about the app use or its tracking. From data pooled from all subjects to date, the total duration of minutes not using the phone shows a negative correlation with the warning signs scale (p=.0001) as well as the length of outgoing phone calls (p=.0024). Taking medications is correlated with the number of outgoing text messages sent (p=.0004).

**Conclusions:** Preliminary sensor data indicates that there are small but statistically significant correlations with psychiatric symptoms for patients with schizophrenia. Results to date also suggest that tracking patients with schizophrenia via their personal smartphone is acceptable in a research context and there is no evidence of harm to date.

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370. High-Throughput Cognitive Phenotyping: Mobile Technology Meets Patient Engagement

**Laura Germine**¹ and Ken Nakayama²

¹Harvard Medical School, ²Harvard University

**Background:** The ability to assess cognition and mental health over the Web and mobile devices provides new opportunities for building research studies that are efficient and highly scalable. This talk will introduce methods for building research tools that enable rapid and precise cognitive phenotyping across very large samples.

**Methods:** We focus here on data collected through TestMyBrain.org, a research website dedicated to participant-centered research studies about the mind and brain. Through TestMyBrain, we have successfully applied principles of software development, user interface design, psychometrics, and participant-centered research to traditional methods and study designs. This allows us to conduct studies that build on previous work, but with much larger and diverse samples, allowing us to generate novel insights about brain and behavior.

**Results:** We describe the characteristics of the 1.6 million people who have participated in research through TestMyBrain.org, along with specific findings from these data that are relevant to understanding cognitive architecture and risk factors for neuropsychiatric disorders. We also give specific examples of how structured A/B testing of particular study and test characteristics has allowed us to improve the psychometric properties of our study tools, at the same time as improving cross-device accessibility and participant engagement.

**Conclusions:** Changes in society and technology permit novel approaches to understanding the brain and mental health. Here, we show how participant-centered, mobile approaches to measuring cognitive and psychiatric phenotypes can help accelerate progress in research and provide greater benefit to participants.

**Keywords:** Neurocognition, cognition, mobile health application, Big data, Endophenotypes

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371. Connected and Open Research Ethics (CORE) Initiative: Engaging Stakeholders to Shape Ethics in the Digital Age

**Camille Nebeker,** Cinnamon Bloss, and Nadir Weibel

UC San Diego

**Background:** Mobile health (mHealth) research utilizing Mobile Imaging, pervasive Sensing, Social media and location Tracking (MISS) technologies like social networks, smartphones apps, and wearable sensors offer the potential to collect unprecedented amounts of real time data captured in free living spaces. These methods introduce new ethical and regulatory challenges for researchers and Institutional Review Boards (IRBs). The Connected and Open Research Ethics (CORE) project is working with stakeholders, including IRBs and scientists, to address these challenges.

**Methods:** The CORE platform is being designed and tested using a participatory approach involving key stakeholders.
Formative research, involving focus groups and key informant interviews, was initiated in fall 2015 to identify features and functionality of the CORE platform.

**Results:** Audio recordings of six focus groups and interviews with 15 key informants were transcribed and analyzed. Results indicate a growing demand for guidance and expertise to evaluate the ethical and regulatory dimensions of research protocols using MISST technologies. Frequently reported challenges include: unfamiliarity with MISST technologies, difficulties determining potential risks and benefits to research subjects, identifying appropriate data management strategies and consideration of bystander rights.

**Conclusions:** MISST research raises new ethical challenges for both scientists and Institutional Review Boards that focus on safety, privacy, bystander rights and data management strategies. Resources discussed will include the CORE Platform and three main features including a: 1- Network 2- Q&A Forum and, 3- Resource Library. Each will be discussed as relevant for biological psychiatry research.

**Supported By:** Robert Wood Johnson Foundation (Principal Investigator: Nebeker, #72876, 2015-2017) and the UC San Diego Supported By:

**Keywords:** mobile health application, ethics, big data, social media, pervasive sensing

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**SYMPOSIUM**

**Network Architectures of the Healthy Brain as Constraints for the Spatiotemporal Patterning of Disease**

Friday, May 19, 2017 - 12:30 PM - 2:30 PM

Aqua 300 AB

Chair: Armin Raznahan
Co-Chair: Mallar Chakravarty

**372. Healthy Developmental and Genetic Brain Modules Influence Maturation Abnormalities in Schizophrenia**

Aaron Alexander-Bloch, Samuel Mathais, Ravi Duggirala, Joanne Curran, John Blangero, and David Glahn

1University of Cambridge, Dept of Psychiatry; 2Department of Psychiatry, University of Cambridge; 3Yale University School of Medicine; 4Department of Neuroimaging, University College London; 5Department of Neuroimaging, University College London; 6Wellcome Trust Centre for Neuroimaging, University College London; 7Department of Clinical Neurosciences, University of Cambridge; 8Research Department of Clinical, Educational and Health Psychology, University College London; 9Wellcome Trust Centre for Neuroimaging, University College London; 10Max Planck Institute for Human Cognitive and Brain Sciences; 11Max Planck Institute for Human Cognitive and Brain Sciences; 12University of Texas Health Science Center

**Background:** Brain network architectures operate in the healthy brain at overlapping biological levels including genetic, developmental and structural connectivity. Schizophrenia, a disorder of brain connectivity and neurodevelopment mediated by genetic risk, may alter or augment these healthy network processes. We tested this notion by comparing spatial patterns of cortical dysmaturation to normative cortical modules defined by developmental and genetic analyses.

**Methods:** This study included two mutually informative MRI samples: ~1500 scans of extended pedigrees living in San Antonio, TX, from the Genetics of Brain Structure and Function study (GOBS); and ~100 childhood-onset schizophrenia (COS) patients and age-matched controls with multiple longitudinal scans, from the COS intramural NIMH study (COS-NIMH). GOBS used SOLAR software to estimate pairwise genetic correlations between the cortical thickness of pairs of macro-anatomic brain regions, which facilitated inter-regional clustering into genetic modules. COS-NIMH used semiparametric regression to model schizophrenia’s effect on cortical thickness growth curves and also derived normative developmental modules composed of regions with convergent maturational trajectories.

**Results:** We found strong evidence for both developmental and genetic modular architectures. Abnormal non-linear growth processes, in a subset of cortical regions in schizophrenia, overlapped with specific genetic and developmental modules that included limbic and prefrontal regions. In contrast, cross-sectional cortical thickness deficits in schizophrenia crossed modular boundaries throughout the cortex.

**Conclusions:** These findings suggest that abnormal cortical development in schizophrenia may be modularized, or constrained by the normal community structure of developmental and genetic brain network architectures, in contrast to the broader diffusion across the cortex evidenced in cross sectional thickness reduction.

**Supported By:** NIMH intramural program; R01 MH078143; R01 MH083824; R25 MH071584

**Keywords:** Brain networks, gene networks, developmental networks, Schizophrenia, Structural MRI
**Background:** Adolescence is a period of human brain growth and high incidence of mental health disorders. The Neuroscience in Psychiatry Network seeks to understand biological underpinnings of the adolescent risk of depression and schizophrenia.

**Methods:** Multi-parametric mapping magnetic resonance imaging was used to measure cortical thickness and intracortical myelination in 297 population volunteers aged 14–24 years old. Regional measures at 308 locations across cortex were combined into a structural covariance network and calculated topological measures of degree and closeness centrality extracted. We related nodal measures to regional gene transcriptome data provided by the Allen Institute for Brain Science (http://human.brain-map.org). All statistical analyses were conducted using permutation tests with significance set at P<.05 after correction for multiple comparisons.

**Results:** We found that association cortical areas were thicker and less myelinated than primary cortical areas at 14 years. Association cortex had faster rates of shrinkage and myelination through adolescence. Adolescent cortical myelination and shrinkage were coupled and specifically associated with a dorsoventrally patterned gene expression profile enriched for synaptic, oligodendroglial- and schizophrenia-related genes. Topologically efficient and biologically expensive hubs of the brain anatomical network had greater rates of shrinkage/myelination and were associated with overexpression of the same transcriptional profile as cortical consolidation. All results replicated in two independent cohorts.

**Conclusions:** We conclude that normative human brain maturation involves a genetically patterned process of consolidating anatomical network hubs. We argue that developmental variation of this consolidation process may be relevant both to normal cognitive and behavioral changes and the high incidence of schizophrenia during human brain adolescence.

**Supported By:** Wellcome Trust 095844/Z/11/Z

**Keywords:** Graph theory, Cortical myelin, Microarray, Adolescence, Oligodendrogenesis

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**374. Circuit-Wide Transcriptional Profiling Reveals Region Specific Gene Co-Expression Networks Regulating Depression Susceptibility**

**Rosemary Bagot**¹, Hannah Cates², Immanuel Purushothaman², Zachary Lorsch², Daniel Geschwind³, Yan Dong⁴, Li Shen⁵, Bin Zhang⁶, and Eric Nestler²

¹McGill University, ²Mount Sinai School of Medicine, ³UCLA, ⁴University of Pittsburgh

**Background:** Depression is a complex and heterogeneous disorder reflecting dysfunction in multiple brain regions. Recent functional studies suggest that opposing alterations in prefrontal cortex (PFC) and ventral hippocampus (VHIP) regulate susceptibility to chronic social defeat stress (CSDS), a highly validated mouse model of depression. The molecular mechanisms mediating depression-associated functional alterations in these brain circuits are largely unknown.

**Methods:** We performed RNA-sequencing on multiple brain regions from control animals and mice susceptible or resilient to CSDS. We employed an intersectional bioinformatics approach combining differential expression with weighted gene co-expression network analyses to identify novel transcriptional networks regulating susceptibility. We used viral-mediated manipulations of identified networks and assessed effects on depression-like behavior, synaptic function and transcriptional regulation.

**Results:** We identified two susceptible-specific gene co-expression networks that exhibited significant enrichment of oppositely regulated genes in PFC and VHIP. Key-driver analysis identified susceptible-specific hub genes in both networks. Viral-mediated over-expression of these genes confirmed bioinformatic predictions of region specific effects. Hub genes, Sdk1 and Dkkl1, increased sEPSC frequency in VHIP, confirming the functional role of these networks in regulating synaptic transmission. Dkkl1 over-expression in VHIP induced expression of other network genes, demonstrating functional connectivity of the co-expression network in vivo and providing molecular validation of our bioinformatics analyses.

**Conclusions:** These results demonstrate that opposing regulation of gene co-expression networks in PFC and VHIP mediates susceptibility. In vivo validation of bioinformatically predicted hub-genes validates the utility of a systems biology approach by identifying novel transcriptional mechanisms that control susceptibility and may offer new leads for antidepressant drugs.

**Supported By:** NARSAD, RO1

**Keywords:** Depression, gene co-expression network, transcription, ventral hippocampus, Prefrontal Cortex

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**375. Charting Dynamic Interactions between Large-Scale Brain Networks in Health and Disease**

**Danielle Bassett**

University of Pennsylvania

**Background:** The human brain is composed of densely interconnected cortical and subcortical modules that evolve significantly over the course of development. Yet, even in adulthood, these modules display nontrivial reconfigurations over short time scales. Understanding these flexible reconfigurations, and their utility in supporting healthy and diseased cognitive function, has remained challenging due to the dearth of appropriate computational techniques.

**Methods:** Here we extend and apply emerging tools from applied mathematics known as multilayer networks to robustly quantify the reconfiguration of cortical and subcortical modules over small time scales. Our advances incorporate principled approaches to model construction, parameter selection, null model formation, and statistic development.

**Results:** We observe that flexible reconfiguration of cortical and subcortical modules is characteristic of diverse cognitive tasks, including the learning of skills and values, the performance of working memory, and the processing of linguistic stimuli in the form of stories. Flexibility differs across anatomical areas, often being lowest in domain-specific areas, and highest in domain-general areas, supporting a core-periphery theory of network utilization. The degree of flexibility varies over individuals, is commonly
associated with individual differences in task performance, and can be modulated pharmacologically. In schizophrenia, flexibility is increased, and intermediate levels of flexibility are observed in first-degree relatives, suggesting that the modular reconfiguration is an intermediate phenotype of the disease. **Conclusions:** Collectively, these studies offer a unique theoretical perspective highlighting the dynamic reconfiguration of brain networks as a key process supporting healthy cognitive function. Moreover, tool set is generally applicable to clinical and translational neuroscience of psychiatric disorders.

**Supported By:** The John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the Army Research Laboratory and the Army Research Office through contract numbers W911NF-10-2-0022 and W911NF-14-1-0679, the National Institute of Health (2-R01-DC-009209-11, R01HD086888-01, R01-MH107235, R01-MH107703, R01-MH108520, 1R01NS099348 and R21-MH-106799), the Office of Naval Research, and the National Science Foundation (BCS-1441502, CAREER PHY-1554488, BCS-1631550, and CNS-1626008).

**Keywords:** graph theory, BOLD fMRI, Schizophrenia, Brain networks, Learning

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**SYMPOSIUM**

**From Translation to Novel Cross-Species Computational Back-Translation of Behavioural Flexibility and Their Relevance to Neuropsychiatry**

Friday, May 19, 2017 - 12:30 PM - 2:30 PM  
Aqua AB  
Chair: Valerie Voon

376. **Subcortical Contributions to the Explore-Exploit Tradeoff**

Bruno Averbeck, Vincent Costa, Daniel Eisenberg, Jasmin Czarapata, Karen Berman, and Elizabeth Murray  
National Institute of Mental Health

**Background:** The explore-exploit trade-off is fundamental to adapting behavior in dynamic environments. When choice options change, one has to decide whether to continue to exploit options of known reward value, or explore novel options. Preference for novelty is often found in compulsive disorders.

**Methods:** We trained monkeys on 3-armed bandit reinforcement learning task in which they learned the values of cues by choosing them and receiving rewards. Periodically, we replaced one of the choice options. We examined how frequently the animals chose each option, while recording neural activity in the amygdala and ventral striatum. We also examined the effects of lesions of these structures on behavior. In addition, we carried out the same task in healthy human subjects, after characterizing aspects of their dopamine system using PET.

**Results:** In the macaques we found increased stimulus related value information in the amygdala, and increased representation of the reward at time of feedback in the ventral striatum, while animals were learning the values of the cues. Lesions of the amygdala increased preference for novel choice options, whereas lesions of the ventral striatum decreased preference for novel choice options. In addition, we found increased FDOPA signaling in the ventral striatum in human participants that were more novelty prone.

**Conclusions:** Novelty preference appears to be mediated by amygdala-ventral striatal circuitry, as well as dopamine innervation of those circuits. The amygdala and ventral striatum may play complementary roles in this behavior. Future work in patient groups may help elucidate the role of these computations in compulsive behaviors.

**Supported By:** NIH ZIA MH002928-01

**Keywords:** reinforcement learning, macaque, amygdala, ventral striatum, dopamine

377. **Trans-Diagnostic Investigation of Behavioral Adaptation in Disorders of Compulsivity – Maladaptive Exploration and Impaired Goal-Directed Behavior**

Andrea Reiter¹, Lorenz Deserno², and Florian Schlagenhauf³  
¹Max Planck Institute, ²Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, Department of Child and Adolescents Psychiatry, Psychotherapy and Psychosomatics, University of Leipzig, ³Charité Universitätssmedizin Berlin, Max Planck Institute for Human Cognitive and Brain Sciences Leipzig

**Background:** BED patients suffer from a lack of behavioral control during recurrent binge eating episodes and, thus, fail to adapt their behavior despite negative consequences. This resembles criteria of substance addiction, which suggests a deficit in goal-directed behavior as a trans-diagnostic feature. Across BED and substance addiction, we investigated two key components underlying goal-directed control: the balance between exploration and exploitation and the use of information not directly experienced.

**Methods:** We exposed BED patients and alcohol-dependent (AD) patients as well as healthy controls to a reward-guided counterfactual reversal learning task during functional resonance imaging (fMRI). We performed fMRI analyses informed via computational modeling of behavior to identify specific signatures of altered decision-making processes in both patient groups.

**Results:** We observed impaired behavioral adaptation in both disorders. Via the use of Reinforcement Learning models we were able to identify different mechanisms underlying this impairment in both patient groups: BED patients showed enhanced, maladaptive exploration behavior. This deficit was accompanied by diminished coding of explorative decisions in the anterior insula/vIPFC. In AD, we observed a deficit to use inference on alternative choice options and their fictive outcomes, particularly after punishment. Neural representation of model-free prediction errors was intact in both patient groups, whereas coding of mPFC learning signatures incorporating abstract inference on un-chosen options was reduced in both disorders.

**Conclusions:** We highlight the important role of computational psychiatry accounts for defining fine-grained neurocognitive phenotypes of different compulsive disorders characterized by impaired goal-directed behavior.
**Keywords**: Addiction, Compulsivity, Goal-directed Behaviour, Binge Eating Disorder, Computational Psychiatry

**378. Disentangling Cause from Consequence: Understanding the Decision-Making Processes Underlying Addiction**

Stephanie Groman1, Bart Massi1, Daeyeol Lee1, and Jane Taylor2

1Yale University, 2Yale University School of Medicine

**Background**: The ability to make adaptive, effective decisions is disrupted in psychiatric disorders such as addiction. These decision-making deficits may be due to dysfunction in processes that enable decisions to be flexible and goal-directed. Recent studies have suggested that model-based, or prospective, learning is impaired in methamphetamine users, but that model-free, or retrospective, learning is unaffected. It's unclear if these decision-making impairments were present prior to drug exposure or were a consequence of chronic drug exposure, and critically what neurochemical disruptions may be mediating specific alterations in decision-making strategies.

**Methods**: To provide insight into the behavioral and neural mechanisms underlying drug-induced decision-making deficits, we assessed decision-making using two novel, operant tasks, adapted from those used in humans, before and after rats were allowed to self-administer methamphetamine for 2 weeks in 6 hour daily sessions.

**Results**: Using reinforcement learning models, we found that natural occurring variation in model-free decision-making processes in a probabilistic, reversal learning and a two-stage decision-making task predicted future methamphetamine-taking behaviors. Rats who were more flexible and able to track changes in reward contingencies, took less methamphetamine than those that were less flexible. Following exposure to methamphetamine, model-free and model-based decision-making were impaired. Neurochemical assessments indicated that the methamphetamine-induced decision-making deficits were due to disruptions in dopaminergic signaling within the nucleus accumbens and serotonin within the orbitofrontal cortex.

**Conclusions**: Together, these data highlight the utility of combining reinforcement learning models with translationally analogous behavioral tasks in rats to provide insight into the behavioral and neural mechanisms that are affected in psychiatric disorders.

**Supported By**: Wellcome Trust

**Keywords**: Dopamine, mu-opioid system, Habit, goal-directed learning, PET imaging

**SYMPOSIUM**

**Neuromodulation with Transcranial Near-Infrared Light: Controlled Evidence**

Friday, May 19, 2017 - 12:30PM - 2:30PM

Aqua C

Chair: Paolo Cassano
Co-Chair: Dan Iosifescu

**380. Transcranial Photobiomodulation for Brain Disorders**

Michael Hamblin

Wellman Center for Photomedicine, Massachusetts General Hospital

**Background**: Transcranial photobiomodulation (tPBM) is a new approach to treat traumatic brain injury (TBI) and many other brain disorders in which NIR light is delivered to the head, and penetrates the scalp and skull to reach the brain.

**Methods**: 810-nm laser was delivered by 1 or 3 daily applications to the heads of mice, with controlled cortical impact TBI. Memory, learning, depression, anxiety were measured for 4 weeks. Mice were sacrificed and immunofluorescence studies carried out on their brains.

**Supported By**: National Institutes of Health (NIH) / National Center for Advancing Translational Sciences (NCATS)

**Keywords**: TBI, photobiomodulation, Optics, imaging
Results: tPBM-treated mice had improved learning and memory, and less depression and anxiety up to 4 weeks. Treated mice had increased neuroprogenitor cells in the dentate gyrus of the hippocampus and subventricular zone at 7 days. Markers of neuron migration and neurotrophins (BDNF) were increased at 7 days, while synaptogenesis (formation of new connections between existing neurons) was increased in the cortex at 28 days.

Conclusions: We propose that tPBM can induce the brain to repair itself after injury. However its ability to induce neurogenesis and synaptogenesis suggests that PBM may have much wider applications to treat neurodegenerative and psychiatric disorders.

Supported By: R01AI050875

Keywords: Traumatic Brain Injury, Neurogenesis, Learning, Major Depression, Transcranial photobiomodulation

381. Transcranial Photobiomodulation: Controlled Evidence for Cerebrovascular and Cognitive Enhancement

Francisco Gonzalez-Lima

The University of Texas at Austin

Background: Transcranial infrared laser stimulation (TILS) is a novel form of brain photobiomodulation. Controlled human studies show that TILS involves up-regulation of cytochrome c oxidase (CCO), the terminal enzyme in mitochondrial respiration, resulting in improved cerebral oxygenation and cognitive and emotional benefits.

Methods: Eight controlled experiments were conducted including a total of 328 participants, 18-40 years old. CW 1,064-nm laser or sham stimulation were administered to the forehead. Laser power was 3.4 W in an area of 13.6 cm², corresponding to 250 mW/cm² irradiance. Two forehead sites were stimulated, 60 J/cm² per site.

Results: Compared with placebo, significant increases (p<0.05, 2-tailed) in cerebral concentrations of oxidized CCO, oxygenated hemoglobin (HbO), total hemoglobin (HbT), and differential hemoglobin (HbD) were all observed during and after TILS in the prefrontal cortex. Furthermore, strong dose-dependent linear interplays between concentration changes in CCO versus HbO and between CCO versus HbT were observed.

Cognitive performance after TILS was significantly enhanced compared to placebo (p<0.05, 2-tailed) in all prefrontal-based measures, including improved reaction time during sustained attention, memory retrieval latency and number of correct responses, executive improvement with fewer errors, better set-shifting ability and rule-based learning. TILS to the right forehead also led to significantly greater (p<0.01, 2-tailed) symptom improvement among depressed participants whose attention was directed away from negative stimuli.

Conclusions: TILS of the human forehead significantly improves cerebral oxygenation and cytochrome c oxidase activity. Randomized controlled trials demonstrated that TILS aimed at the right prefrontal cortex produces significant cognitive and emotional benefits in healthy and depressed populations.

Supported By: University of Texas BRAIN Initiative Seed Funding (#362718) and NIH grants (R03 EB022956 and R21 AG050898).

Keywords: Neuromodulation, Cognitive Performance, Transcranial photobiomodulation, Mood, blood flow

382. Transcranial Photobiomodulation in Major Depressive Disorder

Paolo Cassano

Massachusetts General Hospital

Background: Transcranial photobiomodulation (t-PBM) with red or near-infrared (NIR) light increases brain metabolism and neuroplasticity; it also modulates endogenous opioids, while decreasing inflammation and oxidative stress. Preliminary, uncontrolled studies suggested an antidepressant effect of t-PBM in subjects suffering from major depressive disorder (MDD).

Methods: We conducted a double-blind, sham-controlled study on the safety and efficacy of NIR t-PBM delivered to dlPFC twice in subjects with MDD. The treatment course was 8 weeks of t-PBM (Omnilux New U – LED, 830nm (NIR); 36.2mW/cm²; up to 65.2J/cm²; 3.7kJ per session or sham for a total of 16 sessions). The change in total score of the Hamilton depression rating scale (HAM-D17) from baseline to endpoint was the primary outcome measure (one-way unpaired t-test).

Results: Eighteen evaluable subjects out of 21 randomized were included in the analyses, having received at least 4 t-PBM (real or sham) sessions plus post-treatment assessments. There were no significant differences between groups at baseline. At endpoint, the mean change in HAM-D17 score in subjects receiving t-PBM NIR-mode was significantly greater than sham-mode, both in the overall sample (n=9 vs. 9 sham; p=0.01). The effect size for the antidepressant effect of t-PBM was d=0.87. Further, t-PBM was well tolerated, with no serious adverse events reported.

Conclusions: t-PBM with near-infrared light could be a novel intervention for patients with MDD. Replication in larger samples is warranted.

Keywords: Major Depressive Disorder (MDD), Neuroradiology, Transcranial photobiomodulation, near-infrared radiation, Clinical Trials

383. Transcranial plus Intranasal Photobiomodulation in Mild to Moderately-Severe Dementia

Anita Saltmarche1, Margaret A Naaser2, Kai Fai Ho3, Michael R Hamblin4, and Lew Lim5

1Saltmarche Health & Associates, 2Boston University, Department of Neurology, 3STAT-TU Inc, 4Harvard Medica Schoiol, Wellman Center for Photomedicine, 5Vielight Inc

Background: This case series investigated if patients with mild to moderately-severe dementia, mild cognitive impairment (MCI) or Alzheimer’s Disease (AD) who had baseline Mini Mental State Exam (MMSE) scores of 10-24, would improve when treated with near-infrared (NIR) photobiomodulation (PBM) therapy.
**Methods:** This study used 810nm, 10Hz pulsed, light-emitting diode (LED) devices combining transcranial plus intranasal PBM to treat the cortical nodes of the DMN – e.g., mesial prefrontal, precuneus, angular gyri (transcranial PBM); and hippocampus (intranasal PBM). Five patients with mild to moderately-severe dementia, MCI or AD were entered into 12 weeks of active treatment followed by a 4-week, no treatment period. Patients were assessed with MMSE and Alzheimer’s Disease Assessment Scale–cognitive (ADAS-cog) tests. The protocol involved weekly, in-clinic use of a transcranial plus intranasal PBM device; and daily at-home use of a separate, intranasal-only PBM device.

**Results:** There was significant cognitive improvement after 12 weeks of PBM (MMSE, p<0.003; ADAS-cog, p<0.023). Fewer angry outbursts, better sleep, better daily functioning, less anxiety and wandering were reported. There were no negative side effects. Precipitous declines were observed during the 4-week, no treatment period, a possible problem for future studies. Here, following their completion of study participation each case was given his/her own PBM devices to keep. This case series is the first completed PBM case series to report significant, cognitive improvement in mild to moderately-severe dementia cases post-PBM.

**Conclusions:** Results suggest that larger, controlled studies are warranted. PBM shows potential for home treatment of patients with dementia, MCI, AD.

**Supported By:** Vialight Inc.

**Keywords:** Transcranial and intranasal photobiomodulation

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**SYMPOSIUM**  
**Training Limbic Activity Modulation with Neurofeedback**  
Friday, May 19, 2017 - 12:30 PM - 2:30 PM  
Aqua EF  
Chair: Christian Schmah

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384. Using Functional-Connectivity Neurofeedback to Change Emotion Regulation Networks in Pre-Clinically Anxious Adolescents  
Kathrin Cohen Kadosh¹, Catharina Zich¹, Stephen Lisk², and Jennifer Lau²

¹University of Oxford, Department of Experimental Psychology, ²King’s College London

**Background:** Approximately 1 in 4 children exhibit increased levels of worries and anxiety as they enter adolescence, yet current frontline treatments for paediatric anxiety are only effective in about half of the cases. It has been suggested that early difficulties with emotion regulation go along with an increased risk for developing anxiety, and there is some evidence that the functional coupling between two key emotion regulation regions, the ventro-medial prefrontal cortex (vmPFC) and the amygdala changes during adolescence. Specifically, whereas the mature brain exhibits top-down vmPFC regulation of amygdala reactivity, this specific relationship is only established during late adolescence with research showing that younger children exhibit more positive connectivity between the regions during emotion regulation tasks.

**Methods:** In the current study, we use real-time functional magnetic resonance imaging-based neurofeedback to explore the relationship between plasticity in emotion regulation circuits and anxiety in development. Specifically, we taught a group of pre-clinically high-anxious girls aged 14-16 years to change functional connectivity between the vmPFC and the amygdala.

**Results:** We found that over neurofeedback 4 runs, participants learned to increase the negative functional connectivity between the two regions. We also found that changes in the connectivity between the two regions were driven by changes in vmPFC activation (in 2/3 of the trials), rather than changes in amygdala activation.

**Conclusions:** Our findings support the notion that neurofeedback can be used to change in functional connectivity patterns during development. They also shed some light on the underlying mechanisms, i.e., the relative contribution of the underlying brain regions.

**Supported By:** EC-FP7 No. 602186  
**Keywords:** Adolescence, Anxiety, real-time fMRI neurofeedback, Emotion Regulation

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385. Amygdala-Neurofeedback Reduces Traumatic Stress Vulnerability  
Jackob Keynan¹ and Talma Hendler²

¹Tel Aviv Center for Brain Function, Tel Aviv Sourasky Medical Center, ²Tel Aviv Sourasky Medical Center

**Background:** Amygdala hyper-activation among a-priori healthy individuals, was previously found to predict more post-traumatic symptoms following exposure. Pharmacological and behavioral approaches however do not specifically target the amygdala, possibly explaining the low efficacy of existing therapeutics. The current work tested whether amygdala targeted neurofeedback prior to- or immediately after- traumatic exposure may facilitate emotion-regulation and reduce stress vulnerability. We present results from a large scale (n=160) field study conducted with a-priori healthy Israeli soldiers and preliminary results from a clinical trial conducted with recent trauma survivors.

**Methods:** To enable home stationed training we used a recently developed fMRI-Inspired EEG model of amygdala activity: “The amygdala-electrical-fingerprint” (amyg-EFP). 160 soldiers of combative units were randomly assigned to three groups: (1) Amyg-EFP group training amyg-EFP down-regulation, (2) A/T group training down-regulation of alpha/theta ratio, and (3) No-treatment group continuing military training without neurofeedback. Additional civilian group of recent trauma survivors underwent either amyg-EFP or A/T neurofeedback. Participants underwent six neurofeedback sessions including clinical, neural and psychological outcome measures.

**Results:** Relative to the control groups, following training the amyg-EFP group exhibited improved emotion-regulation and lower stress vulnerability as indicated by self-report questionnaires and an emotional-stroop task. Post-training fMRI revealed that the amyg-EFP group also exhibited lower amygdala reactivity in response to threat cues and higher functional connectivity of the amygdala with the mPFC.
Preliminary results further indicated that amyg-EFP neurofeedback may alleviate stress symptoms among recent trauma survivors.

**Conclusions:** These results demonstrate the promising potential of amygdala targeted neurofeedback as a preventive or early intervention of traumatic stress.

**Supported By:** US DOD, EU Seventh Framework

**Keywords:** fMRI, EEG, PTSD, Emotion-Regulation, Clinical-Trial

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**386. Plastic Modulation of Intrinsic Neural Networks in PTSD through Amygdala Downregulation via Real-Time fMRI Neurofeedback**


**Clinical Trials**

**Background:** Large scale neural networks, such as the default mode network (DMN), salience network (SN), and central executive (CE) network, have been shown to be altered in patients with posttraumatic stress disorder (PTSD), where electroencephalography neurofeedback has been shown to plastically modulate these networks. Using real-time fMRI neurofeedback, downregulation of the amygdala during PTSD symptom provocation has been shown to increase amygdala connectivity with prefrontal executive functioning regions. However, changes in large scale neural network intrinsic connectivity during amygdala downregulation has not yet been investigated in PTSD.

**Methods:** Patients (n = 15) completed 3 sessions of real-time fMRI neurofeedback, with the instruction to down regulate the amygdala while viewing personalized trauma words. Amygdala downregulation was assessed by contrasting a) regulate trials, with b) viewing trauma words and not attempting to regulate. Training was followed by one transfer run without neurofeedback. Independent component analyses were used to explore functional connectivity within the SN, CE, and DMN.

**Results:** PTSD patients were successfully able to downregulate their amygdala, displaying both increased connectivity within the SN and CE and decreased connectivity within the DMN. Changes in the intrinsic functional connectivity of these networks were negatively correlated to PTSD symptoms.

**Conclusions:** This is the first demonstration that amygdala downregulation using real-time fMRI neurofeedback results in network connectivity changes within PTSD patients. This suggests that amygdala downregulation is targeting neural networks that may be related to a spectrum of clinical symptoms observed in PTSD, including cognitive dysfunction (CE), arousal/interoception (SN), and an altered sense of self (DMN).

**Supported By:** Canadian Institutes for Veterans and Military Health #W7714-125624/001/SV

**Keywords:** Posttraumatic Stress Disorder, real-time fMRI neurofeedback

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**387. Training Amygdala-Prefrontal Networks with Neurofeedback in Borderline Personality Disorder**

**Christian Paret**, Gabriele Ende, Jenny Zähringer, Matthias Ruf, and Christian Schmahl

**Clinical Trials**

**Background:** With functional magnetic resonance imaging neurofeedback (NF), amygdala activity is visualized in real time. The neural circuitry of emotion dysregulation can be targeted with this technique. Limbic hyper-responsiveness is characteristic for conditions with heightened affective lability, such as Borderline Personality Disorder (BPD). Training patients to down-regulate limbic brain activity with NF directly involves dysregulated networks and may be beneficial in future treatment.

**Methods:** Data from two completed and two ongoing experiments will be reported. Participants with BPD and participants without a psychiatric diagnosis were presented with amygdala NF while viewing emotional pictures. Feedback was given by a thermometer presented besides the pictures. The instruction was to down-regulation the amplitude of the thermometer display.

**Results:** Patients and healthy controls were successful in down-regulating their amygdala response. Prefrontal-limbic connectivity was increased with neurofeedback. Patients with BPD reported a decrease in dissociation and increase in emotional awareness over the course of four sessions. New results will be reported, aiming to give a broader understanding of the neural mechanisms behind brain self-regulation with amygdala NF.

**Conclusions:** NF is instrumental in understanding neural mechanisms of emotion and brain self-regulation. In line with others, our findings are in accord with a potential therapeutic benefit. Ongoing studies try to establish transfer effects of amygdala NF on different measures of emotion processing and regulation.

**Supported By:** German Research Foundation (DFG)

**Keywords:** Borderline Personality Disorder, real-time fMRI neurofeedback, Amygdala, Emotion Regulation

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**ORAL SESSION**

**Neuroimaging and Related Methods in Mood Disorders**

**Friday, May 19, 2017 - 12:30 PM - 2:30 PM**

**Aqua 311 AB**

**Chair:** Jorge Almeida

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**388. A Complex Networks Approach to the Symptomatology of Mood Disorders**

**Baktash Babadi**, Ji Hyun Baek, and Andrew Nierenberg

**Clinical Trials**

**Background:** Conventional psychiatric diagnosis, based on criteria such as DSM-IV, might come short of providing a full picture of the disorders due to methodological limitations.
Alternatively, the complex network approach can provide important knowledge about the interrelation of symptoms. Here, we examine such an approach in the context of major mood disorders.

**Methods:** We analyzed over 43,000 individuals from the National Epidemiologic Survey of Alcohol and Related Condition (NESARC). Cases with Major Depressive Disorder (MDD) (N = 5,695), Bipolar I Disorder (BP-I) (N = 1,411), and Bipolar II Disorder (BP-II) (N= 493) were extracted. Networks were constructed for the whole NESARC and each of the above diagnoses, using MatLab: symptoms were represented by “nodes”, and correlations between them by the “links”; nodes were arranged into clusters with a mechanical analogue. The centrality of each node was calculated as an index of cardinality of the corresponding symptom.

**Results:** In MDD, BP I and BP II, the anxiety cluster accompanies depressive or manic symptoms, implying high degree of co-morbidity. The social phobia cluster is prominent in both phases of BP-I. The depressive cluster is tighter in BP-II than BP-I, implying more symptomatic depressive episodes in the former. The major cardinal symptom of depression (whether bipolar or unipolar) is fatigue. In BP-I/ manic, the major cardinal symptom is distractibility, while in BP-II/hypomanic it is elevated mood.

**Conclusions:** Network analysis reveals important aspects of the symptomatology of mood disorders beyond the conventional criteria-based diagnostic approach.

**Keywords:** Mood disorders, Complex networks, Network Cluster, mood symptoms

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Irina Esterlis, Robert Pietrzak, Nicole DellaGioia, David Matuskey, Henry Huang, John Krystal, Ronald Duman, Richard Carson, and Sjoerd Finnema

Yale University

**Background:** Evidence from postmortem and preclinical studies of cell pathologies in depression strongly implicates reductions in synaptic density in the prefrontal cortex (PFC) in the pathophysiology of MDD. For the first time in vivo, we examined PFC synaptic density in individuals with depression as compared to controls using radiotracer 11C-UCB-J and positron emission tomography (PET), and assessed whether lower PFC synaptic density is associated with increased depression and cognitive deficits.

**Methods:** Ten individuals with MDD (mean age=39) and 7 healthy controls (mean age=35) participated in 11C-UCB-J PET to measure synaptic density. The arterial input function was measured for quantification of volume of distribution (VT). Radiotracer was injected as a bolus, and subjects were scanned for 90 minutes. In the rodent experiment, the rodents were exposed to stress for 21 days and synaptic density was quantified postmortem.

**Results:** We observed lower synaptic density in individuals with depression as compared to control individuals in the dorsolateral PFC (dlPFC, 17% lower) and ventromedial PFC (vmPFC, 15% lower). Lower dlPFC synaptic density was associated with greater depressive symptomatology (p = 0.03) and poorer performance on delayed verbal recall (p = 0.05). In rodents, stress reduced levels of synaptic density in the PFC compared to control rats by 12%.

**Conclusions:** The preliminary in vivo results support the hypothesis that PFC synaptic density is lower in depression and that this alteration is associated with some of the mood and cognitive deficits observed in the disorder. Normalizing synaptic density may be a potential mechanism to provide relief to individuals with MDD.

**Supported By:** VA NCPTSD, Nancy Taylor Foundation, K01

**Keywords:** PET imaging, Depression

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**390. Internal and External Expectancies Shape Placebo-Induced Activation of the Salience Network in Depression**

Marta Pecina1, Joseph Heffernan2, Erich Avery3, Kristen Villalobos4, Jonathan Wilson5, Howard Aizenstein1, and Alex Dombrovski1

1University of Pittsburgh, 2University of Wisconsin, 3University of Michigan

**Background:** Expectancies biased toward positive outcomes have proven to be a powerful mechanism to evoke internal healing: the placebo effect. Still, the neural and cognitive mechanisms through which expectancies translate into subjective improvement, particularly in depression, are not well understood. We hypothesized that both, internal and external expectancies shape the response to placebos through the activation of the salience network, recruiting brain regions commonly implicated during the response to antidepressant treatments.

**Methods:** Twenty patients with major depression underwent the simulated real-time neurofeedback (NF) fMRI experiment, during the i.v. infusions of a “fast-acting antidepressant treatment” (i.v. saline). Briefly, the task included six 12-trial runs, where each trial began with a 10-second timer cue reflecting the anticipation of drug infusion/no infusion, followed by 12 seconds of positive/negative NF along with a filling bar graph, representing the drug infusion/no-infusion. At each trial, subjects rated their expected and actual mood improvement, which were analyzed using mix-effects models. Voxel-wise BOLD signal was analyzed using AFNI’s 3dDeconvolve (p<.05 FWE-corr).

**Results:** Feedback ratings were significantly influenced by external cues [positive simulated NF (t[1350]=4.65, p<.0001)] and the expectation ratings (t[1350]=3.21, p=.001). Expectations ratings were significantly influenced by the exposure to infusion (t [1236]=4.75, p<.001). Whole-brain analyses revealed that the simulated neurofeedback elicited responses in the left insula, ventral and dorsal striatum, thalamus, dorsal anterior cingulate and occipital cortex.

**Conclusions:** Our results detail the contributions of external and internal expectancies in the formation of placebo responses in patients with depression, which appear to depend on the activity of the salience network and the striatum.

**Supported By:** K23MH108674

**Keywords:** Placebo Effects, Neuroimaging, Depression, Salience Network, Learning
391. A Brain Model of Disturbed Self-Appraisal in Depression

Christopher Davey¹, Michael Breakspear², Jesus Pujo³, and Ben Harrison¹

¹University of Melbourne, ²Queensland Institute of Medical Research, ³Hospital 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, though it remains unclear how functional alterations of the region contribute to the observed disturbances. The aim of the 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 magnetic resonance imaging data from 71 youth with moderate-to-severe major depressive disorder, none of whom were being treated with medication, and 88 healthy control participants. Bayesian modeling averaged was used to determine parameter estimates for the dynamic causal models, which were compared between groups.

Results: While self-directed cognitive processes in depression were shown to rely on the same dynamic network as in healthy controls, the medial prefrontal cortex had a ‘hyper-regulatory’ effect on posterior cingulate cortex in the depressed participants, with self-appraisal causing significantly more negative modulation of connectivity between medial prefrontal cortex and posterior cingulate cortex than in the controls (odds ratio=0.55, 95% CI 0.39 to 0.77; p=0.0006). This parameter was inversely related with a depression factor related to poor concentration and inner tension (r=-0.32; 95% CI -0.57 to -0.09; p=0.01).

Conclusions: The exaggerated influence of the medial prefrontal cortex on posterior cingulate cortex in depression is a neural correlate of the disturbed self-appraisal that is characteristic of the illness.

Supported By: National Health and Medical Research Council (Australia)

Keywords: Depression, Self-reflection, Youth, fMRI, Neural Networks

392. Fractal Dimension (FD) of Resting EEG is a Prospective Biomarker for Treatment Response to Electroconvulsive Therapy (ECT)

Natasha Singh and Mohammed Warsi

McMaster University

Background: Electroconvulsive therapy (ECT) remains one of the most effective treatments available for severe depression. However, robust predictors of response are needed to identify patients who will benefit from ECT and guide personalized treatment. Recent research has identified fractal dimension (FD) analysis as a valuable tool for characterizing the complexity of biological signals. The FD of ictal and postictal EEG has been found to correlate with ECT treatment response. In this naturalistic study we investigated whether responders and nonresponders to ECT had differing fractal characteristics of resting EEG prior to treatment.

Methods: Resting two-channel (FP1, FP2) EEG data (n=14) were acquired immediately prior to the subject’s first ECT treatment. Artifact-free 6-second epochs were analyzed using detrended fluctuation analysis, resulting in a FD value for each channel. At the end of their course of ECT, subjects were classified into two groups: responders and nonresponders, with ECT response defined as a greater than 50% reduction in Patient Health Questionnaire (PHQ-9) score.

Results: At baseline, responders to ECT had significantly lower FDs (t=-2.23, p=0.046) with the effect size being considered large (Cohen’s d=1.15). This result was present in both prefrontal channels.

Conclusions: This study is the first describing the relationship between fractal measures of baseline resting EEG and ECT outcomes. Responders to ECT had lower EEG FDs, which is indicative of decreased neurophysiological complexity. These preliminary results suggest that FD has the potential to serve as a prognostic biomarker to inform ECT treatment decisions.

Keywords: Electroconvulsive therapy (ECT), Fractal Dimension, Biomarkers, Electroencephalography

393. Reduced Inhibitory Influence of Insula Cortex upon the Limbic System in Individuals at High Familial Risk of Mood Disorder with Depression

Liana Romaniuk¹, Jessika Sussmann¹, Tiffany Stewart¹, Alix MacDonald¹, Stephen Lawrie¹, Jeremy Hall², Andrew McIntosh¹, and Heather Whalley¹

¹University of Edinburgh, ²University of Cardiff

Background: Bipolar disorder (BPD) and major depressive disorder (MDD) likely involve dysconnectivity between limbic and regulatory cortical regions. The influence genetic risk has on this network remains unclear.

Methods: Participants from the prospective, longitudinal Scottish Bipolar Family Study (people age 16-25 at high familial risk of BPAD and controls), performed an implicit emotional memory task during fMRI, viewing positively- and neutrally-valenced scenes, with recall assessed outside the scanner (n=128). Individuals were grouped into: healthy controls who remained well throughout the course of the study (HC, n=51); high risk who also remained well (HR-well, n=57); and high risk who met diagnostic criteria for MDD either at the time of the scan or developed MDD within 2 years (HR-ill, n=20). Data were analysed according to the percentage of emotional and neutral scenes correctly recalled. The influence of top-down regulatory mechanisms on limbic activation was assessed using dynamic causal modelling (DCM).

Results: Right posterior hippocampus showed a group x valence interaction, with HR-ill demonstrating aberrant activation association with poor recall of emotional stimuli. DCMs indicated that insula inhibited the connection between fusiform (sensory) and amygdala in HC, which then projects to hippocampus. This inhibition was progressively less present in HR-well and HR-ill F(2,127) = 3.204, p = 0.044).
Conclusions: Those at genetic risk with MDD demonstrated aberrant hippocampal activation during an emotional memory task. This was potentially driven by a lack of insula’s inhibitory influence between sensory cortex and amygdala, which in turn directly influenced hippocampal activation.

Supported By: Wellcome Trust; Royal College of Physicians of Edinburgh; Health Foundation; NARSAD; Scottish Funding Council; NHS Research Scotland; Sackler Foundation; European Union’s Seventh Framework Programme

Keywords: Emotional Memory, familial risk, longitudinal cohort, Mood disorders, Dynamical Causal Modeling

394. Development and Preclinical Evaluation of [18F]JNJ-64413739 as a PET Radioligand for P2X7 Receptors

Hartmund Kolb1, Wei Zhang2, Gang Chen2, Chunfang Xia2, Katrin Szardenings2, Anindya Bhattacharya2, Brian Lord3, Michael Letavic2, and Jose I. Andres3

1Johnson & Johnson / Janssen Research & Development, 2Janssen R&D, 3Janssen

Background: The P2X7 receptor is an adenosine triphosphate (ATP)-gated ion-channel. P2X7R activation leads to the release of the pro-inflammatory cytokine IL-1b in the brain and as such the P2X7 receptor may play a role in neuroinflammation. Herein we describe the development of [18F]JNJ-64413739, a 18F-labelled PET ligand for imaging the P2X7 receptor.

Methods: The P2X7R affinity and specificity, pharmacokinetics, metabolic stability, BBB permeability, and off-target binding of JNJ-64413739 were evaluated. The labeled radiotracer [18F]JNJ-64413739 was synthesized by nucleophilic aromatic substitution. The specific binding of [18F]JNJ-64413739 was evaluated through a series of in vitro autoradiography (ARG) experiments with rodent brain tissue sections. The P2X7R tracer was also studied in rhesus macaques.

Results: The potency of JNJ-64413739 is 1.9 nM and 1.0 nM at the recombinant rat and human P2X7 receptor (IC50s, FLIPR), respectively, and the binding affinity is 2.7 nM (Ki, rat cortex binding assay) and 15 nM (Ki, human P2X7r). In vitro ARG blocking experiments with [18F]JNJ-64413739 demonstrated inhibition of tracer binding to rat brain tissue sections in a dose-dependent manner by two P2X7R antagonists. Non-human primate PET imaging studies (two rhesus monkeys) revealed dose-dependent receptor occupancy (RO) of JNJ-54175446.

Conclusions: JNJ-64413739 is a potent and selective ligand for rat and human P2X7R. In vitro ARG experiments with hP2X7R rats and WT/KO mice brain sections suggested that [18F]JNJ-64413739 engaged the P2X7 receptor. Reproducible and dose-dependent RO of JNJ-54175446 was obtained in rhesus monkeys by PET imaging with [18F]JNJ-64413739. This PET tracer exhibits dose-dependent RO of JNJ-54175446 was obtained in rhesus monkeys and WT/KO mice brain sections suggested that [18F]JNJ-64413739 was synthesized by nucleophilic aromatic substitution. In vivo ARG experiments with [18F]JNJ-64413739 demonstrated inhibition of tracer binding to rat brain tissue sections in a dose-dependent manner by two P2X7R antagonists. Non-human primate PET imaging studies (two rhesus monkeys) revealed dose-dependent receptor occupancy (RO) of JNJ-54175446.

Keywords: Neuroinflammation, Positron Emission Tomography, P2X7R, Radiotracer

395. Anterior Cingulate Cortex Morphology Predicts Treatment Response to Internet-Based CBT for Depression

Christian Webb1, Elizabeth Olson1, William D.S. Killgore2, Diego Pizzagalli1, Scott Rauch1, and Isabelle Rosso1

1Harvard Medical School and McLean Hospital, 2University of Arizona

Background: Rostral anterior cingulate cortex (rACC) activity has been shown to predict depressive symptom improvement across different antidepressant treatments. This study extends prior work by examining whether rACC morphology predicted treatment response to internet-based cognitive behavioral therapy (iCBT) for major depressive disorder (MDD).

Methods: Hierarchical linear modeling (HLM) tested whether pre-treatment rACC volume predicted self-reported (Patient Health Questionnaire–9; PHQ-9) depressive symptom improvement during a 10-week randomized clinical trial of iCBT (n = 37) vs. a monitored attention control (MAC; n = 40). We also tested whether pre-treatment rACC volumes differed between depression remitters vs. non-remitters (using the Hamilton Rating Scale for Depression; HRSD). The PHQ-9 was completed 8 times over the course of treatment; whereas the HRSD was administered at pre- and post-treatment.

Results: Larger right (F[1,32.2] = 8.47, p < 0.01), but not left (F[1,32.2] = 0.56, p = 0.46), rACC volume was a significant predictor of greater PHQ-9 symptom improvement in iCBT, even when controlling for demographic (age, gender, race) and clinical (baseline depression, anhedonia and anxiety) variables previously linked to treatment response. In addition, pre-treatment right (F(1,16) = 6.01, p = 0.03), but not left (F(1,16) = 0.31, p = 0.59), rACC volume was larger among iCBT patients whose depression remitted relative to those who did not remit. Corresponding analyses in the MAC group were not significant.

Conclusions: For MDD patients, rACC volume prior to iCBT demonstrated incremental predictive validity beyond clinical and demographic variables previously found to predict symptom improvement. If replicated, such morphological measures could be integrated into clinical care to inform treatment decision-making.

Supported By: USAMRAA Award W81XWHC12C0109 (Rauch); NIMH K23 MH108752 (Webb); NIMH R01: MH096987 (Rosso)

Keywords: Anterior Cingulate Cortex, Prediction of Treatment Outcome, Internet, Cognitive Behavior Therapy, Randomized controlled trial

ORAL SESSION
Clinical/Translational Neuroscience of Psychosis and Related Disorders - #2
Friday, May 19, 2017 - 3:00 PM - 5:00 PM
Aqua 300 AB
Chair: Erica Duncan

396. Neuroplasticity Benefits of Adding Aerobic Exercise to Cognitive Training in First-Episode Schizophrenia Patients

Sarah McEwen, Behnaz Jarrahi, Kenneth Subotnik, Joseph Ventura, and Keith Nuechterlein

UCLA Department of Psychiatry & Biobehavioral Sciences
Background: Schizophrenia patients experience debilitating cognitive dysfunctions that serve as a barrier in their returning to full work or social functioning. Current pharmacologic treatments in schizophrenia have limited success in remediating cognitive deficits. Both aerobic exercise and cognitive training separately have been found to increase neuroplasticity and improve cognitive functioning to a moderate degree in schizophrenia. This is the first study to examine the effects of a combined exercise and cognitive training intervention on brain plasticity in first-episode schizophrenia patients.

Methods: MRI scans were collected at UCLA to extrapolate cortical thickness and resting-state fMRI measurements at baseline and 6-month follow-up in 37 first-episode schizophrenia patients randomly assigned to combined cognitive training and exercise (CT&E, N = 20) or cognitive training without exercise (CT, N = 17) for 6 months. The MCCB cognitive battery was also administered at baseline and 6 months.

Results: Significant Group x Time interactions for cortical thickness were found in prefrontal regions (left DLPFC, superior frontal gyrus and right medial orbitofrontal cortices). The CT&E group showed improved functional connectivity, compared to the CT group, between the right central executive network (CEN) and the ventral attention network and also between the left CEN and right CEN. Improved functional connectivity between the left and right CEN was associated with cognitive gains in Reasoning and Problem Solving at 6-month follow-up.

Conclusions: These structural and functional connectivity findings highlight the additive role of exercise to bolster increases in cortical thickness and lead to more efficient functional organization in the PFC, which was related to improvements in executive functioning.

Supported By: K01MH1094931 (PI: S. McEwen) and R34MH102529 (PI: K. Nuechterlein)

Keywords: exercise intervention, MRI, Resting State, First-Episode Psychosis (FEP), Cognitive Training

396. Aerobic Exercise Training in People with Schizophrenia: Neural, Cognitive, and Functional Benefits

David Kimhy1, Julia Vakhrusheva2, Matthew N. Bartels3, Jacob S. Ballon4, Eero Castrén5, and Richard P. Sloan6

1Columbia University & New York State Psychiatric Institute, 2Weill Cornell Medical College, Department of Psychiatry, 3Albert Einstein College of Medicine, Department of Rehabilitation Medicine, 4Stanford University, Department of Psychiatry and Behavioral Sciences, 5University of Helsinki, Neuroscience Center, 6Columbia University, Department of Psychiatry

Background: Schizophrenia is associated with cognitive deficits that have been identified as major determinants of poor daily-functioning. Findings from basic-science and clinical populations have linked cognitive improvements to increases in aerobic fitness (AF) via aerobic exercise training (AE). Such improvements have been attributed to up-regulation of brain-derived neurotrophic factor (BDNF). Yet, the impact of AE on cognition and daily-functioning, and the role of BDNF, have not been investigated in schizophrenia.

Methods: Eleven stable individuals with schizophrenia spectrum disorder with moderate-to-severe IIA (≥3 PANSS G12, X = 4.8, SD = 1.2) and 10 healthy controls participated in a double-blind, crossover, randomized controlled pilot, feasibility study. Participants received two MRIs: (i) Arterial spin labeling (ASL) to measure rCBF, and (ii) fMRI task designed to assess illness denial, pre and post dual-hemisphere parietal (cathode left P3/anode right P4) or sham tDCS carried out in the scanner.

Results: Consistent with our original fMRI study, IIA was associated with activation in the left PPA at the moment of illness denial. Further, parietal tDCS increased rCBF in the underactive right PPA (15 min post-tDCS, t = 3.21, p = 0.004).

Conclusions: Serial dual-hemisphere parietal tDCS appears to be a feasible approach to increase rCBF and brain activity in PPA associated with IIA, in turn, restoring interhemispheric balance and improving IIA in schizophrenia.

Supported By: Ontario Mental Health Foundation grant (OMHF) Type A Grant; Ontario AHSC AFP Innovation Fund (MOHLTC)

Keywords: Insight into illness, Illness Awareness, Schizophrenia, transcranial Direct Current Stimulation, Functional MRI

397. TDCS Modulates Brain Regions Associated with Impaired Illness Awareness in Schizophrenia Spectrum Disorders

Philip Gerretsen, Eric Piltman, Julie Kim, Jun Chung, Shinichiro Nakajima, Youssef Alshehri, Fernando Caravaggio, Yusuke Iwata, Daniel Blumberger, Bruce Pollock, and Ariel Graff-Guerrero

Centre for Addiction and Mental Health, University of Toronto

Background: Impaired illness awareness (IIA) is common among individuals with schizophrenia, contributing to medication non-adorherence and poor treatment outcomes. Transcranial direct current stimulation (tDCS) is thought to increase and decrease neuronal excitability under the anode and cathode, respectively. Our prior fMRI work suggests IIA in schizophrenia is associated with activation in the left posterior parietal area (PPA) and increased connectivity in the default mode network with the left PPA. In this pilot feasibility study, we aimed to determine if single session dual-hemisphere parietal tDCS would increase regional cerebral blood flow (rCBF) in the underactive right PPA and/or reduce rCBF in the overactive left PPA to restore interhemispheric balance.

Methods: Eleven stable individuals with schizophrenia spectrum disorder with moderate-to-severe IIA (≥3 PANSS G12, X = 4.8, SD = 1.2) and 10 healthy controls participated in a double-blind, crossover, randomized controlled pilot, feasibility study. Participants received two MRIs: (i) Arterial spin labeling (ASL) to measure rCBF, and (ii) fMRI task designed to assess illness denial, pre and post dual-hemisphere parietal (cathode left P3/anode right P4) or sham tDCS carried out in the scanner.

Results: Consistent with our original fMRI study, IIA was associated with activation in the left PPA at the moment of illness denial. Further, parietal tDCS increased rCBF in the underactive right PPA (15 min post-tDCS, t = 3.21, p = 0.004).

Conclusions: Serial dual-hemisphere parietal tDCS appears to be a feasible approach to increase rCBF and brain activity in PPA associated with IIA, in turn, restoring interhemispheric balance and improving IIA in schizophrenia.

Supported By: Ontario Mental Health Foundation grant (OMHF) Type A Grant; Ontario AHSC AFP Innovation Fund (MOHLTC)

Keywords: Insight into illness, Illness Awareness, Schizophrenia, transcranial Direct Current Stimulation, Functional MRI
daily-functioning were correlated ($r=.51, p=.01$). Fidelity with target training intensity, but not frequency/duration, was correlated with cognitive improvement ($r=.70, p=.02$).

**Conclusions:** The results indicate AE is effective in enhancing cognitive and daily-functioning in people with schizophrenia and provide support for the impact of AE-related BDNF up-regulation on cognition in this population. Low AF represents a modifiable risk-factor for cognitive dysfunction in schizophrenia for which AE training offers a safe, non-stigmatizing, and side-effect-free intervention.

**Supported By:** The National Institute of Mental Health, 1R21MH096132

**Keywords:** Schizophrenia, cognition, BDNF, Aerobic exercise, Functioning

399. Ketamine and Guanfacine Effects on Activation and Connectivity during Working Memory: A Functional Magnetic Resonance Imaging Investigation

**Naomi Driesen,** Gregory McCarthy, Amy Arnsten, Peter Morgan, George He, Michael Bloch, and John Krystal

**Yale University School of Medicine**

**Background:** Preclinical research indicates that alpha2 adrenergic agonists close HCN channels in the prefrontal cortex (PFC) thus improving working memory (WM). We hypothesized that guanfacine would reduce WM-related neural deficits produced by the NMDA antagonist ketamine. In particular, we hypothesized that guanfacine would alter the activation and connectivity of the PFC and locus coeruleus (LC), areas rich in alpha2 adrenergic receptors.

**Methods:** 14 healthy volunteers participated in two MRI scans. They received three 1 mg guanfacine pills or equivalent saline placebo. During scanning, they performed a spatial WM task and received saline followed by ketamine infusion. The ketamine infusion consisted of a bolus (0.23 mg/kg over 1 minute) followed by a constant infusion 0.58 mg/kg/hr and the saline infusion was of equal size and duration. All results were significant at $p<0.05$, unless otherwise stated. Connectivity was assessed with voxelwise statistical maps cluster-corrected with voxel-wise and cluster-wise significance of 0.05.

**Results:** Guanfacine did not affect ketamine-associated changes in symptoms and WM performance nor activation in WM areas. Under saline, guanfacine increased intra-PFC connectivity during task compared to placebo; but, under ketamine, it decreased it. Guanfacine marginally ($p=0.07$) reduced ketamine-associated decrements in LC activation to the WM task. Under saline, it altered the usual, negative correlation between LC and PFC activity to weakly positive. No interaction between ketamine and guanfacine was observed on task-related LC connectivity.

**Conclusions:** This study provides initial evidence of guanfacine’s effects on PFC and LC connectivity and activation with and without ketamine.

**Supported By:** National Center for Post-traumatic Stress Disorder, Yale CTSA grant UL1TR000142 (NCATS, NIH)

**Keywords:** Working memory, Noradrenergic System, psychosis, NMDA antagonists, Prefrontal Cortex

400. Dysfunctional Emotion Discrimination in Schizophrenia is Associated with HSV-1 Infection and Improves with Antiviral Treatment

**Vishwajit Nimgaonkar**1, Triptish Bhatia2, Joel Wood3, Satish Iyengar2, Sreelatha Narayana2, Konasale Prasad1, Kehui Chen3, Robert Yolken4, Faith Dickerson5, Ruben Gur6, Raquel Gur6, and Smita Deshpande7

1University of Pittsburgh School of Medicine, 2Dr. Ram Manohar Lohia Hospital, New Delhi, India, 3Western Psychiatric Institute & Clinic, University of Pittsburgh, 4Johns Hopkins School of Medicine, 5Sheppard Pratt Hospital, 6University of Pennsylvania, 7Dept. of Psychiatry, Centre of Excellence in Mental Health PGIMER-Dr. Ram Manohar Lohia Hospital, New Delhi, India

**Background:** Herpes simplex virus, type 1 (HSV-1) produces intermittent lytic, productive infection in many organs, alongside lifelong, latent infection in neurons. HSV-1 infected individuals have greater cognitive dysfunction than uninfected individuals, particularly persons with schizophrenia – even without encephalitis. We investigated whether HSV-1 related cognitive dysfunction is progressive or remediable.

**Methods:** In a prospective naturalistic follow up sample (PNFU), temporal changes in cognitive functions were analyzed in relation to baseline HSV-1 infection in persons with or without schizophrenia (N=226). Separately, in a randomized controlled trial (RCT), HSV-1 infected, clinically stabilized outpatients with SZ received Valacyclovir (VAL, an antiviral, 1.5 G twice daily for 16 weeks) or placebo (PLA) added to standard antipsychotic treatment, using a stratified randomization design, following placebo run-in (N=67). In both samples, HSV-1 infection (seropositivity) was estimated using serum IgG antibodies. All clinical evaluations were blinded to HSV-1 or treatment. Standardized Z scores for accuracy on eight cognitive domains were analyzed for temporal trajectories using generalized linear models (PNFU) and VAL/PLA differences compared with intent to treat analyses (RCT).

**Results:** PNFU: At baseline, HSV-1 infected participants had significantly lower accuracy scores for Emotion Identification and Discrimination (EMOD), Spatial memory and Spatial ability (p=0.025, 0.029, 0.046, respectively), regardless of SZ diagnosis. They also had a significantly steeper temporal worsening for EMOD (p=0.03), RCT: EMOD improved significantly in VAL-treated patients (p=0.048, Cohen’s d=0.43).

**Conclusions:** HSV-1 infection is associated with time-related dysfunction in EMOD, which indexes social cognition. Conversely, VAL treatment improves EMOD. A portion of HSV-1 associated cognitive dysfunction is progressive, but remediable.

**Supported By:** NIH, Stanley Medical Research Institute

**Keywords:** cognition, HSV-1, Schizophrenia, Emotion, valacyclovir

401. Discriminant Validity of the Patient-Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS): A Novel Outcome Measure for Schizophrenia Research

**Raymond Rosen**1, Jeremiah Trudeau2, Steven Silverstein3, David Henderson4, Bernet Kato1, and Michael Sand2

1University of Pittsburgh School of Medicine, 2Yale University, 3University of Pennsylvania, 4Collaborative Clinical Research, Inc.
Background: We have previously described the development and content validity of a new patient-reported outcome measure (PRO): The Patient-Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS). We report here on known-groups validity testing and the sensitivity of PRECIS to between-group differences, comparing patients with schizophrenia and age-matched controls.

Methods: The PRECIS PRO is a 35-item scale comprising eight concept domains (memory, communication, control, planning, handling problems, attention, sharp thinking and overall experience), each with multiple individual items. PRECIS was administered to an independent sample of psychiatrically healthy control subjects (single visit), and at the randomization visit for a subset of patients in a large, clinical trial assessing patients with schizophrenia on stable antipsychotic treatment (NCT02281773).

Results: PRECIS was completed by 88 control subjects and 412 patients with schizophrenia, with few missing data. The total PRECIS score was significantly lower for control subjects compared with patients (mean [standard deviation (SD)] score: 1.39 [0.7] vs 2.06 [1.2]; p < 0.0001), as was the global rating measure of cognitive impairment (overall experience, 1.41 [0.7] vs 2.35 [1.3]; p < 0.0001). For each domain of patient experience, PRECIS mean scores were also significantly lower for control subjects compared with patients with schizophrenia (range of mean differences: -0.94 [overall experience domain] to -0.52 [control domain]; p < 0.0001, all domains). The attention domain discriminated most sensitively between control subjects and patients (mean [SD] scores: 1.68 [0.8] vs 2.47 [1.3]; p < 0.0001).

Conclusions: The PRECIS PRO demonstrated robust discriminant validity in this study, and is being further tested for use in clinical research and practice in schizophrenia.

Supported By: Boehringer Ingelheim. Editorial assistance was provided by Natasha Thomas of Fishawack Communications.

Keywords: Cognition, Patient-Reported Outcome, Subjective Experience, Validation

403. Investigation of Superior Longitudinal Fasciculus Fiber Complexity in Recent-Onset Psychosis

Philip Szewzko1, Ek Tsoon Tan2, Aziz Ulug3, Juan Gallego4, Kathryn Rhindress5, Anil Malhotra6, Delbert Robinson6, and Luca Marinelli2

1Ichahn School of Medicine at Mount Sinai, 2GE Global Research, 3CorTech Labs, Inc, 4Weill Cornell Medical College, 5New York University School of Medicine, 6Feinstein Institute for Medical Research

Background: Diffusion tensor imaging (DTI) performs well in regions consisting of a single fiber direction, but cannot resolve fiber tracts aligned along different axes. We used diffusion spectrum imaging to determine whether abnormalities in the superior longitudinal fasciculus (SLF) play a role in the neurobiology of psychosis while considering crossing white matter fiber complexity.

Methods: Twenty-seven (20M/7F) patients with recent-onset psychosis and 23 (11M/12F) healthy volunteers completed a diffusion spectrum imaging (DSI) scan. Dependent measures included the number of fiber directions, defined as the total number of peaks located on the orientation distribution function; a model-independent, multi-directional anisotropy (MDA) metric that is superior to FA in its sensitivity to underlying water diffusion; fractional anisotropy (FA) and tract volume.

Results: We identified significant group x hemisphere interactions for the number of fiber directions, MDA and FA. Patients demonstrated a significant reversal in the normal (R>L) asymmetry of fiber directions and a lack of normal (L>R) asymmetry in FA and MDA compared to healthy volunteers.
Patients had a significantly greater number of crossing fibers, lower MDA and lower FA in the left SLF compared to healthy volunteers. The number of fiber directions in both the right and left SLF was significantly and inversely correlated with FA in each respective hemisphere among healthy volunteers.

**Conclusions:** Our findings provide the first in-vivo evidence for abnormal crossing white matter fibers within the SLF among individuals with psychosis. A reversal in the normal pattern of white matter asymmetry in patients may be consistent with an aberrant neurodevelopmental process.

**Supported By:** R01 MH076996

**Keywords:** Diffusion Spectrum Imaging, Psychosis, Diffusion Tensor Imaging, Crossing Fibers, Superior Longitudinal Fasciculus

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### ORAL SESSION - MIXED TOPICS #1

**Friday, May 19, 2017 - 3:00 PM - 5:00 PM**

**Aqua 310 AB**

**Chair:** Ebrahim Haroon

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#### 404. The Effectiveness of an Emotional Working Memory Training in Borderline Personality Disorder

**Annegret Krause-Utz**$^1$, Julia-Caroline Walther$^1$, Susanne Schweizer$^2$, Stefanie Lis$^1$, Tim Dalgleish$^2$, Christian Schmah$^1$, and Martin Bohus$^1$

$^1$Central Institute of Mental Health, $^2$Medical Research Council Cognition and Brain Sciences Unit, Cambridge, United Kingdom

**Background:** Emotion dysregulation, associated with altered heart rate variability (HRV) and increased emotional distractibility, are core features of Borderline Personality Disorder (BPD). The purpose of this study was to evaluate the effectiveness of a computerized Emotional Working Memory (EWM) training on self-reported well-being and HRV during an emotion regulation paradigm in BPD.

**Methods:** In a randomized control trial, 50 BPD patients were randomly assigned to the EWM training group (dual-n-back-task with emotional faces as distractors, n=25) or a placebo training (feature match WM task, n=25). At baseline and after 26-day training, participants performed two tasks measuring cognitive control of disturbing emotional material: 1) an adapted Sternberg working memory paradigm (with neutral vs. negative distractors, EWM), and 2) a cognitive emotion regulation (reappraisal task). Changes in working memory performance, subjective arousal ratings, and HRV data were assessed as primary outcome measures.

**Results:** Both training groups improved in working memory performance during the EWM (F(1,46)=5.73, p=.021, n$^2$=.11). Patients who underwent the EWM training, reported a significant improvement in the down-regulation of negative emotions during the emotion regulation paradigm (as compared to passively attending negative pictures) compared to the placebo training group (significant interaction effect Time by Group: F(1,47)=4.98, p=.030, n$^2$=.10). Moreover, a significant correlation between training success and self-reported emotion regulation and changes in HRV were found.

**Conclusions:** These novel unpublished findings suggest that the Emotional Working Memory training may be a promising add-on intervention, showing a beneficial effect on self-reported emotion regulation in BPD.

**Keywords:** Borderline Personality Disorder, Emotional working memory training, Heart rate variability, Emotion Regulation, randomized control study design

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#### 405. HIV Alters PTSD Symptomology and Psychophysiology in Traumatized Women

**Gretchen Neigh**$^1$, Vasiliki Michopoulos$^2$, Igbo Ofotokun$^2$, and Tanja Jovanovic$^2$

$^1$Virginia Commonwealth University, $^2$Emory University

**Background:** HIV-infected individuals are exposed to high rates of trauma that can lead to the development of posttraumatic stress disorder (PTSD). However, it remains unclear how HIV infection influences PTSD presentation in trauma-exposed individuals.

**Methods:** All participants (n=42, 25 HIV-, 17 HIV+) were women between 18 and 48 years old recruited from Grady Memorial Hospital in downtown Atlanta, GA, and provided informed consent. Lifetime trauma history was determined by the 14-item Traumatic Events Inventory (TEI), which assesses for experiencing and witnessing traumatic events. Childhood trauma history was assessed via the Childhood Trauma Questionnaire (CTQ). The PTSD Symptom Scale (PSS) was used to determine current overall PTSD symptoms. A sub-set of subjects also participated in a fear-potentiated startle (FPS) paradigm.

**Results:** Women with HIV (HIV+) exhibited higher levels of re-experiencing (F=12.19, p=0.001) and avoidance (F=8.12, p=0.007) PTSD symptoms compared to the HIV- group, after controlling for trauma exposure. HIV+ women also showed impaired fear conditioning in the FPS paradigm compared to the traumatized controls (interaction effect of HIV and Trial Type, F=7.34, p=0.03). While the HIV- women showed a typical increase in startle magnitude to the CS+, that was previously paired to an aversive stimulus (F=23.75, p=0.003), the HIV+ women exhibited a deficit in fear conditioning, even after controlling for trauma exposure (p>0.05). Specifically, HIV+ women did not show FPS to the danger signal (CS+).

**Conclusions:** Taken together, these preliminary data indicate that HIV is associated with altered PTSD symptom presentation and fear learning deficits in traumatized women.

**Supported By:** MH110364

**Keywords:** HIV, PTSD, Inflammation, Women, Chronic Stress

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#### 406. Tracing the Neural Carryover Effects of Anger and their Relation to Traumatic Stress Symptoms

**Gadi Gilam**$^1$ and Talma Hendler$^2$

$^1$Tel Aviv Center for Brain Function, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center, $^2$Tel Aviv Sourasky Medical Center
406. Somatic Symptoms Historically Termed “Post-Concussive” are Common in the Weeks after Sexual Assault but Unrelated to Head Injury

Byron Maltez1, Jenyth Sullivan1, April Soward1, Teresa D’Anza2, Kathy Bell3, Lynn Galloway3, Megan Lechner4, Aryn Gieger-Sedgwick5, Jennie Buchanan6, Jeffrey Ho7, Catherine Rossi8, Kimberly Hurst9, Ralph Riviello10, Amanda Corzine11, Theresa Moriarty12, and Samuel McLean1

1Institute for Trauma Recovery, University of North Carolina at Chapel Hill, 2Albuquerque SANE Collaborative, 3Tulsa Forensic Nursing Services, 4Memorial Health System, 5Crisis Center of Birmingham, 6Denver Health, 7Hennepin County Medical Center SARC, 8Cone Health, 9Wayne County SAFE, 10Philadelphia SARC, 11KentuckyOne Health SAFE Services, 12MedStar Health Research Institute

Background: “Post-concussive” somatic symptoms (e.g., dizziness, headache, nausea) are common after trauma/stress exposure. The population attributable fraction of post-concussive syndrome (PCS) due to direct brain trauma versus neurobiologic stress system activation remains poorly understood.

Methods: Women ≥18 years of age presenting within 72 hours of sexual assault to one of the 12 US sites in the Better Tomorrow Network were enrolled. Post-concussive symptoms (Rivermead Post Concussion Symptoms Questionnaire) were assessed one and six weeks after sexual assault. At week 1, post-concussive symptoms prior to assault were also assessed. Based on WHO definition, PCS presence was defined as ≥3 worsening post-concussive symptoms vs. baseline. Head trauma was determined

407. Sex Differences in Anatomical Connectivity Networks Associated with Obesity

Arpana Gupta, Emeran Mayer, Kareem Hamadani, Connor Fling, Kirsten Tillisch, Bruce Naliboff, Claudia Sanmiguel, and Jennifer Labus

The Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress and Resilience at UCLA

Background: The brain plays a central role in regulating ingestive behavior in obesity. The imbalance in processing rewarding and salient stimuli, similar to addiction behaviors, results in eating behaviors that override homeostatic needs. We performed network analysis to examine the association between body mass index (BMI) and network measures of integrity, information flow, and global communication (centrality) in reward, salience and sensorimotor networks, and to identify sex-related differences in these parameters.

Methods: Structural and diffusion tensor imaging were obtained in a sample of 124 individuals. Graph theory was applied to calculate anatomical network properties (centrality) for regions of the reward, salience, and sensorimotor networks. General linear models with linear contrasts were performed to test for BMI and sex-related differences in measures of centrality, after controlling for age.

Results: Obesity was associated with greater global connectedness of reward and salience network regions in males and females. Sex differences were observed in individuals with high BMI, with females having greater centrality in reward and salience regions, but males having greater centrality in reward and sensorimotor regions.

Conclusions: In individuals with increased BMI, reward, salience, and sensorimotor network regions are susceptible to topological restructuring. These findings highlight the influence of these regions on integrative processing of food-related stimuli and increased ingestive behavior in obesity. The relationship between brain restructuring and obesity depends on sex, demonstrating the importance of considering sex differences in obesity pathophysiology.

Supported By: K23 DK106528 (AG), R01 DK048351 (EAM), P50 DK064539 (EAM)

Keywords: Obesity, Sex differences, anatomical architecture, graph theory, Reward network
using history and physical data obtained at the early post-assault forensic exam.

**Results:** To date in this ongoing study, 299 and 189 sexual assault survivors have completed initial and full study enrollment; 104 sexual assault survivors had medical record data extracted and entered. 74/104 (71%) were conscious throughout the entire assault (to provide head trauma history), and 58/74 (78%) had reached/completed six week follow-up. PCS was very common after sexual assault [68/74 (92%) at 1 week, 44/58 (76%) at 6 weeks]. The great majority of women with PCS at these timepoints had no head trauma [55/68 (81%) at 1 week, 33/44 (75%) at 6 weeks], and head injury was not associated with PCS presence.

**Conclusions:** PCS is the norm in the weeks after sexual assault; however the great majority of “post-concussive” syndrome cases are not due to head trauma.

**Supported By:** RO1AR064700

**Keywords:** post-concussive, sexual assault

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**409. Both Odor Identification and Amyloid Status Predict Memory Decline in Older Adults**

William Kreisig, Peng Jin, Seonjoo Lee, Ezra Dayan, Shankar Vallabhajosula, Gregory Petilon, Leslie Shaw, and Davangere Devanand

1New York State Psychiatric Institute, 2Columbia University Medical Center, 3Weill Cornell Medical Center, 4University of Pennsylvania

**Background:** Odor identification impairment predicts cognitive decline in older adults. We compared the predictive utility of University of Pennsylvania Identification Test (UPSIT) scores to central nervous system β-amyloid status for future memory decline.

**Methods:** Eighty-four adults (age 68 ± 4.7 years; 58 with amnestic mild cognitive impairment and 26 controls) had UPSIT, cognitive testing, and PET imaging with 11C-Pittsburgh Compound B (PIB) and/or lumbar puncture at baseline, plus at least 6 months’ follow-up. We compared UPSIT to three determinants of β-amyloid-positivity: composite PIB standardized uptake value ratio (SUVR) > 1.5, PIB SUVR > 1.2, or CSF Aβ42 < 250 pg/mL.

**Results:** At follow-up, 67% of participants showed memory decline. In subjects that underwent PET imaging (n = 77), UPSIT < 35 predicted memory decline (OR = 3.668, 95% CI = 1.136, 11.955, p = 0.030), as did both PIB > 1.5 (OR = 16.177, 95% CI = 1.802, 145.188, p = 0.013) and PIB > 1.2 (OR = 4.179, 95% CI = 1.234, 14.154, p = 0.022). In subjects that underwent lumbar puncture (n = 42), both UPSIT < 35 (OR = 8.310, 95% CI = 1.049, 65.805, p = 0.045) and CSF Aβ42 < 250 pg/mL (OR = 5.489, 95% CI = 1.133, 26.590, p = 0.034) predicted memory decline. Combining UPSIT and β-amyloid status did not improve prediction of decline. UPSIT correlated with PIB binding (r = 0.4582, p < 0.0001); concordance between low UPSIT and positive β-amyloid status was 53-67%. In patients with MCI, UPSIT (p < 0.05), but not PIB PET, predicted cognitive decline (p < 0.05).

**Conclusions:** UPSIT predicts memory decline as well as PIB PET or CSF Aβ42 levels. Low UPSIT in the highest PIB SUVR group, and in patients with amnestic MCI, argues that UPSIT can be a useful biomarker for cognitive decline in the initial clinical stages of Alzheimer’s disease.

**Supported By:** National Institute of Aging

**Keywords:** olfaction, mild cognitive impairment, PET amyloid imaging, cerebrospinal fluid, cognitive decline

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**410. Empirical Categories of Common Dimensions of Psychopathology in Youth and their Neurocorrelates**

Joel Stoddard, Katharina Kircanski, Simone Haller, Kendra Hinton, Banafsheh Sharif-Askary, Susan Zhang, Kenneth Towbin, Argyris Stringaris, Daniel S. Pine, Ellen Leibenluft, and Melissa A. Brotman

1University of Colorado Anschutz Medical Campus, Children’s Hospital, 2Emotion Development Branch, National Institute of Mental Health, National Institutes of Health

**Background:** Common dimensions of psychopathology often co-occur, and such co-occurrence may have a neural basis. Recently, we determined broad categories of co-occurring dimensions of psychopathology in youth (Kircanski et al., 2016). Here, in a subsample, we explore the associations of such categories to neural activation during implicit face-emotion processing.

**Methods:** Participants were 201 youth, 8-18 years (165 psychiatric outpatients and 36 healthy volunteers). During fMRI, they labeled the gender ofEkman faces with 3 Emotions (angry, happy, fearful) at 3 Intensities of expression (50%, 100%, and 150%). Agreement between latent profile analysis and singular value decomposition categorized the youth by parent- and self-report measures of anxiety, depression, inattention/hyperactivity, and irritability. BOLD fMRI data for correct trials were analyzed by multivariate modeling with Category, Emotion, and Intensity as predictors. Results were whole brain, cluster corrected at p<0.05.

**Results:** Four Categories emerged: (1) low levels of all symptoms (LOW); (2) high levels of all symptoms (HIGH); (3) predominant irritability and inattention/hyperactivity (IRR/ADHD); and (4) predominant anxiety and depression (ANX/DEP). Category by Emotion activation was significant in the right dorsolateral prefrontal cortex (dPFC) (xyz = 46.2,18.8,31.2, F(6,389.8) = 5.17, p<0.001) and right fusiform gyrus (xyz = 41.2,56.2, -16.2, F(5.9,383.4) = 5.11, p<0.001). In the dPFC, ANX/DEP and IRR/ADHD youth exhibited opposing patterns of activation to fearful faces. In the right fusiform gyrus, HIGH youth exhibited hypoactivation to fearful faces relative to LOW and ANX/DEP youth.

**Conclusions:** Four categories of co-occurring dimensions of psychopathology emerge in the current and parent sample. These categories have distinct neural responses to fearful faces, adding to their discriminant validity.

**Supported By:** NIMH Intramural Research Program

**Keywords:** Cluster Analysis, Symptom Dimensions, BOLD fMRI, children and adolescence, Facial Emotion

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**411. Dose-Dependent Social-Cognitive Effects of Intranasal Oxytocin Delivered with Novel Breath Powered Device in Adults with Autism Spectrum Disorder: A Randomized Placebo-Controlled Double-Blind Crossover Trial**

Daniel Quintana, Lars Westlye, Sigrun Hope, Terje Nærland, Knut Smerud, Ramy Mahmoud, Per Djupesland, and OleAndreassen

Background: The neuropeptide oxytocin has shown promise as a treatment for symptoms of autism spectrum disorders (ASD). However, research progress has been hampered by a poor understanding of oxytocin’s dose-response and sub-optimal intranasal delivery methods. We have previously shown in a dose-response trial that a low dose of oxytocin (8IU) modulates social cognition in neurotypical individuals, but research has yet to examine the dose-response in ASD.

Methods: We examined two doses of oxytocin, delivered using a novel Breath Powered intranasal delivery device designed to improve direct nose-to-brain activity, in a double-blind, crossover, randomized, placebo controlled trial. In a randomized sequence of single-administration sessions, 17 male adults with ASD received 8IU oxytocin, 24IU oxytocin, or placebo followed by social-cognitive tasks.

Results: We observed a main effect of treatment on the primary outcome measure of emotion salience measured by emotional ratings of faces (F=3.49, p=0.04), which was associated with a large effect size (p<0.18). Posthoc tests (adjusted for multiple comparisons) revealed that compared to placebo, 8IU treatment increased emotion salience (p=0.02, d=0.63). There was no significant increase after 24IU treatment (p=0.12, d=0.4). Effects after 8IU oxytocin were observed despite no significant increase in peripheral blood plasma oxytocin concentrations (p=0.45).

Conclusions: This is the first trial to assess the dose-dependent effects of a single oxytocin administration in ASD. Results indicate that a low, but not higher, dose of oxytocin can significantly modulate emotion salience despite minimal systemic exposure. The data provide further support that oxytocin treatment may help ameliorate a core ASD feature.

Supported By: Research Council of Norway; OptiNose AS, Novo Nordisk Foundation

Keywords: Oxytocin, Autism Spectrum Disorder, Clinical Trials, Dose Response, Social Cognition

SYMPOSIUM
Effects of Childhood Maltreatment on Connectivity, Functional Networks and Brain Network Architecture in Susceptible, Resilient and Recovering Individuals
Friday, May 19, 2017 - 3:00 PM - 5:00 PM
Sapphire AB
Chair: Martin Teicher

412. Longitudinal Neurodevelopmental Trajectories in Pediatric PTSD
Taylor Keding1, Sara Heyn2, Julian Motzkin2, Jeanette Mumford2, and Ryan Herringa1
1University of Wisconsin School of Medicine & Public Health, 2University of Wisconsin – Madison, 3University of California - San Francisco

Background: Prior neuroimaging studies of pediatric PTSD, using cross-sectional designs, suggest abnormalities in threat processing networks. However, longitudinal neuroimaging studies are critical for identifying neurodevelopmental trajectories which could serve as indicators of recovery and illness persistence.

Methods: We examined fronto-limbic structure and intrinsic connectivity longitudinally in 22 medication-free youth with PTSD and 21 healthy comparison (HC) youth, ages 8-18. Youth completed structural and resting-state MRI at baseline and one year later. T1 images were analyzed using longitudinal voxel-based morphometry (VBM) in SPM12. Resting-state connectivity was conducted in AFNI using amygdala seeds. Linear mixed-effects analyses examined group differences over time, adjusted for age/sex, with whole-brain correction. Posthoc analyses examined the relationship between neurodevelopmental differences and symptom change.

Results: In the VBM analysis, a group by time interaction in left dorsolateral prefrontal cortex (dlPFC) revealed decreasing dPFC volume in HC, consistent with normative cortical thinning, but not in PTSD youth. DLFC volume at time 2 was positively associated with hyperarousal symptoms in PTSD youth. In the resting-state analysis, a group by time interaction for left amygdala-dorsomedial (dm)PFC (k=627) showed less positive/more negative coupling over time in HC, with the reverse pattern in PTSD. Furthermore, amygdala-dmPFC connectivity was positively related to hyperarousal symptoms in PTSD youth.

Conclusions: These findings reveal abnormal neurodevelopmental of prefrontal cognitive control networks in pediatric PTSD which may underlie persistence of heightened threat responses. These results offer developmentally informed targets of intervention that could be employed in future studies to improve outcomes in pediatric PTSD.

Supported By: K08 MH100267; NARSAD Young Investigator Grant; AACAP Junior Investigator Award

Keywords: Childhood Trauma, structural neuroimaging, Resting state fMRI, pediatric PTSD, Longitudinal Brain Imaging

413. Resting State Functional Connectivity of the Innate Alarm System in PTSD
Sherain Harricharan1, Daniela Rabellino1, Paul Frewen1, Maria Densmore1, Jean Theberge2, Allan Schore3, and Ruth Lanius1
1Western University of Canada, 2Lawson Health Research Institute, 3University of California Los Angeles

Background: In lieu of consciously appraising the threat via cortical sensory processing, a subcortical ‘innate alarm system’ originating in the superior colliculus (SC) may activate innate defensive responses when threat is imminent. Individuals with posttraumatic stress disorder (PTSD) demonstrate supra- and subliminal threat detection, together contributing to hyperarousal symptoms and increased defensive responses. Here, the periaqueductal gray (PAG) may work in tandem with the SC to initiate instinctual defensive strategies. The current study was designed to examine functional connectivity patterns with the PAG and the SC at rest in PTSD and healthy controls.
Methods: We examined PAG and SC resting-state functional connectivity in PTSD (n=107) and healthy controls (n=61) using a seed-based approach via PickAtlas and SPM12.

Results: Both healthy controls and PTSD patients showed widespread SC functional connectivity patterns with pre-motor and V1 cortical regions at rest. Notably, these SC connectivity patterns were stronger in controls. By contrast, virtually no PAG functional connectivity was observed in controls. However, PTSD patients further demonstrated extensive PAG functional connectivity with brain regions associated with emotional reactivity and defensive posturing (e.g., anterior insula, cingulum, pre/post central gyrus).

Conclusions: These findings suggest that although the SC has extensive connections at rest in both controls and PTSD, the PAG may also be responsible for additional defensive posturing at rest. These findings emphasize the importance of identifying functional connectivity of the innate alarm system and related brain stem structures in PTSD.

Supported By: Canadian Institutes of Health Research #137150 and #97914

Keywords: Functional MRI, Resting State, Posttraumatic Stress Disorder

414. Susceptible and Resilient Maltreated Individuals Have Comparable Global Network Abnormalities but Differ in Amygdala Centrality

Kyoko Ohashi, Carl Anderson, Elizabeth Bolger, Cynthia McGreenery, Alaptagin Khan, and Martin Teicher

McLean Hospital, Harvard Medical School

Background: Childhood maltreatment (CM) affects brain development and is a major risk factor for psychopathology. Initially we thought that psychiatric and neurobiological resilience would go together, so that maltreated individuals with psychopathology (susceptible) would differ neurobiologically from healthy controls, but maltreated individuals without psychopathology (resilient) would not. However, this appears not to be the case, at least in terms of regional brain size. A key question is whether psychiatrically resilient maltreated individuals have alterations in brain network architecture and unique abnormalities that may enable them to compensate for these differences.

Methods: Right-handed, unmedicated subjects were recruited from the community. CM was assessed using the MACE. Diagnosis and current symptom scores were assessed using SCID I & II and Kellner Symptom Questionnaire. Brain network architecture (90 nodes template) was established using DTI, tractography and graph theory.

Results: Network architecture was evaluated in 263 subjects (73% female, 18-25 years). Participants with moderate to high CM differed from subjects with low exposure in number of interconnected regions (p<0.01), global efficiency (p<0.03) and small-worldness (p<0.005). Differences from controls were even more apparent in resilient than susceptible participants. Susceptible and resilient subjects did however differ in centrality of their right amygdala (degree: p<0.03; closeness: p<0.05), which was more interconnected in susceptible individuals.

Conclusions: Reduced centrality of the right amygdala (relative to both controls and susceptible subjects) may be a compensatory adaptation that enables some maltreated individuals to maintain mental well-being despite marked changes in global network architecture. Compensatory mechanisms may provide novel therapeutic insights.

Supported By: RO1 DA017846, RO1 MH091391 and donation from Susan Miller to MHT.

Keywords: childhood maltreatment, Resting state functional, Diffusion Tensor Imaging (DTI), Amygdala

415. Childhood Maltreatment, Major Depression and the Dorsal Nexus

Martin Teicher, Carl Anderson, Alaptagin Khan, Cynthia McGreenery, Elizabeth Bolger, and Kyoko Ohashi

McLean Hospital

Background: Sheline et al (2010) proposed that the cognitive control, default mode and affective networks had increased connectivity to the same bilateral dorsal medial prefrontal cortical (PFC) region in depressed individuals, and that linkage through this expanded ‘dorsal nexus’ provided a mechanism to explain how disparate symptoms of major depression (MDD) (i.e., decreased ability to focus on tasks, rumination, excessive self-focus, increased vigilance, and emotional, and autonomic dysregulation) could occur concurrently and behave synergistically. This finding however, was based on a small sample (n=35 total). Our aim was to ascertain in a larger sample whether there was a significant association between dorsal nexus size and severity of depression and degree of exposure to peer emotional abuse – a primary risk factor for MDD.

Methods: Resting state functional connectivity was collected in 329 (127M/202F) right-handed, unmedicated individuals 21.8±2.5 years of age recruited from the community and analyzed using dorsolateral PFC, precuneus and subgenual - pregenual cingulate seeds. Type and timing of exposure to maltreatment and severity of depression were assessed using MACE scale and Kellner’s Symptom Questionnaire, respectively.

Results: Size of the dorsal nexus correlated with severity of depression (β=0.14, p=0.01). Further, we found that dorsal nexus size correlated with degree of peer emotional abuse at ages 14 (β=0.10, p<0.05) and 15 (β=0.13, p<0.007) based on multiple regression.

Conclusions: These findings provide additional support for the potential role of the ‘dorsal nexus’ in MDD as well as a mechanism to explain why exposure to peer emotional abuse during adolescence may be a potent risk factor.

Supported By: RO1 DA017846, RO1MH091391 and donation from Susan Miller to MHT.

Keywords: Maltreatment, Resting state functional connectivity, Major Depression, peer bullying, Default Mode Network

Carlos Zarate, Allison Nugent, Rodrigo Machado-Vieira, Jennifer Evans, Jessica Reed, and Lawrence Park
National Institute of Mental Health

Background: The use of the rapid-onset antidepressant ketamine could facilitate our understanding of the neurobiology of the response and relapse processes found in mood disorders.

Methods: We present data on the recently completed Ketamine ‘MOA’ study in where 34 drug-free MDD/TRD patients and 25 healthy controls completed a crossover trial with i.v. ketamine 0.5 mg/kg or placebo 2 weeks apart. Multi-modal biological assessments were collected longitudinally throughout the study to capture the neurobiology of response and relapse. Biological assessments included sMRI, fMRI, DTI, MRS, polysomnography, magnetoencephalography, metabolomics, and miRNA.

Results: Significant decreases in depressive, anxiety, and anhedonia symptoms were seen with ketamine compared to placebo. Blood oxygen level dependent (BOLD) signal during the dot probe task revealed a significant interaction between group, drug, and emotion in bilateral anterior cingulate (ACC) that extended to areas of the medial frontal and superior frontal gyri. Specifically, depressed subjects showed greater activation than controls in response to angry faces, which decreased following the ketamine infusion. Our findings suggest that a negative processing bias at baseline in prefrontal cortical areas is absent following ketamine in patients with MDD, as compared to healthy volunteers, potentially indicating that ketamine normalized the emotional processing bias that characterized MDD. In an analysis of resting state fMRI, connectivity with the default mode network was increased following ketamine infusion in the insula, thalamus/pulvinar, MT and ACC, which are areas involved in the salience network.

Conclusions: Preliminary findings suggest promising insights into the neurobiology of MDD, and the neural correlates of the response to ketamine.

Supported By: National Institute of Mental Health

Keywords: Depression, Neurobiology, Antidepressant response, Ketamine, Glutamate

417. Recent Trial Data from Nitrous Oxide Effects in Treatment-Resistant Depression

Charles Conway, Peter Nagele, and Peter Nagele
Washington University School of Medicine in St. Louis

Background: Treatment-resistant major depression (TRD), major depressive disorder (MDD) that fails to respond to a series of antidepressant trials, remains poorly understood and difficult to treat. N-methyl-D-aspartate antagonists (e.g., ketamine) have demonstrated acute antidepressant efficacy in TRD, including in a recent double-blind, placebo-controlled study of inhaled nitrous oxide (N2O). This presentation will present existing data on the use of N2O in TRD, including preliminary pilot data, a recent N2O dose-finding study, and brain network changes associated with N2O exposure.

Methods: A double-blind, placebo-controlled design was employed in the pilot N2O TRD study. All TRD subjects received either placebo or 50% N2O; depression assessments were performed pre-treatment, and 2 and 24 hours post-treatment. To obtain data on dose optimization, TRD patients received (double-blind) three doses of N2O concentration, 0% (placebo), 25%, and 50%. A neuroimaging study was employed to examine network-based functional connectivity magnetic resonance imaging (fcMRI); assessments compared functional connectivity changes occurring after N2O exposure in three brain networks linked to MDD.

Results: The pilot study demonstrated 50% inhaled nitrous oxide was effective in rapidly reducing TRD depressive symptoms; data detailing differences with alternative dosing will be presented. Additionally, functional neuroimaging connectivity changes brought about by N2O inhalation will be detailed.

Conclusions: 50% inhaled N2O has demonstrated TRD antidepressant efficacy. Animal studies suggest lower percentages may be effective. Reductions in functional connectivity in regions critical in depression (the dorsal nexus, default mode, and prefrontal cortex affective circuits) have been demonstrated with NMDA antagonists (e.g., ketamine) and may occur with N2O.

Supported By: R21 MH108901; Brain & Behavior Research Foundation (Independent Investigator Award); McDonnell Center for Systems Neuroscience

Keywords: Major Depression, Treatment Resistant Depression, nitrous oxide, NMDA antagonists

418. Five Year Open Label Study of Vagus Nerve Stimulation vs. Treatment as Usual in Severe Treatment Resistant Depression

Scott Aaronson1, Peter Sears2, Frances Ruvuna2, and Mark Bunker2

1Sheppard Pratt Health System, 2LivaNova

Friday Abstracts
Background: There is scant evidence to guide treatment for patients who have failed more than four somatic therapies for depression and less to inform chronic management of these patients. A multi center, open label, prospective TRD registry was undertaken to follow the clinical outcome for 5 years in TRD patients receiving either treatment as usual only (TAU) or with adjunctive Vagus Nerve Stimulation (VNS).

Methods: Eligible patients included adults experiencing a current major depressive episode (unipolar or bipolar) and failed at least 4 antidepressant treatments. Primary efficacy endpoint was the response rate based on MADRS.

Results: The VNS Therapy arm and TAU arm consisted of 494 and 301 patients, respectively. Statistically significant improvement in MADRS scores in the VNS Therapy arm versus TAU arm was noted when comparing response rate through 5 years of follow up (67.8% versus 40.2%; p <0.001). Patients in the VNS Therapy arm were more likely to experience remission than patients in the TAU arm over a 5 year period (43.4% versus 24.6%; p <0.001). Significant separation was also seen in both ECT responders and non-responders, bipolar depressives and patients with co-morbid anxiety.

Conclusions: The registry is the first to comprehensively and prospectively collect long term information on the clinical course for patients with severe TRD. Overall findings demonstrate that adjunctive VNS Therapy results in significantly better outcomes over a 5 year period compared to TAU alone in this disabled patient population.

Supported By: Cyberonics (now LivaNova)

Keywords: TRD, VNS, Long term, neurostimulation

419. Inflammation in Treatment Resistant Depression: Challenges and Opportunities

Charles Raison

School of Human Ecology, University of Wisconsin-Madison

Background: Major depressive disorder (MDD) is associated with elevations in a number of peripheral inflammatory biomarkers. Consistent with this, activation of the body’s inflammatory response system—especially when chronic—promotes the development of depressive symptoms in concert with changes in brain and neuroendocrine function that are commonly observed in MDD. Taken together, these findings have often been interpreted to mean that MDD is an inflammatory condition. This insight has fueled current large-scale efforts to develop anti-inflammatory agents as novel antidepressants.

Methods: While not disputing the potential relevance of these efforts, the current talk will review recent evidence suggesting that the association between immune and brain function relevant to depression is neither linear, nor simple, and that simplified explanations of depression as an inflammatory condition may do as much harm as good for the treatment of MDD.

Results: We present data from our group, as well as relevant animal data, suggesting that many depressed individuals may benefit from acute stimulation of at least certain aspects of the inflammatory response.

Conclusions: If confirmed, these findings suggest a more nuanced view of brain-immune interactions that might help devise precision medicine approaches to the use of immune modulators to treat MDD.

Supported By: Brain & Behavior Research Foundation (Independent Investigator Award), the Depressive and Bipolar Disorder Alternative Treatment Foundation, the Institute for Mental Health Research, the Braun Foundation and from Barry and Janet Lang and Arch and Laura Brown

Keywords: Major Depression, inflammation, cytokines, hyperthermia, infliximab

SYMPOSIUM

Schizophrenia through fMRI’s Prism: Brain Network Dysfunction and the Pathophysiology of the Illness

Friday, May 19, 2017 - 3:00 PM - 5:00 PM

Sapphire IJ

Chair: Ivy Tso


Ivy Tso1, Mike Angstadt1, Beier Yao2, Vaibhav Diwadkar3, and Stephan Taylor3

1University of Michigan, 2Michigan State University, 3Wayne State University Medical School

Background: Abnormal eye gaze perception in schizophrenia is associated with compromised social functioning. However, the unknown neural mechanisms limit our ability to design effective interventions. This study used dynamic causal modeling (DCM) of fMRI data to reveal aberrant dynamics between brain regions during eye gaze perception in schizophrenia.

Methods: Twenty-five patients with schizophrenia (SZ) and 20 healthy controls (HC) completed a gaze perception task during BOLD fMRI. Participants viewed faces with different gaze angles and decided the gaze direction or gender. Four nodes showing differential activation between Gaze and Gender were identified for DCM: secondary visual cortex (Vis), temporo-parietal junction (TPJ), anterior insula (alsn), and medial prefrontal cortex (mPFC). A bilinear model space was generated with these 4 nodes, as well as visual input of face, self-connections, bidirectional connections between nodes, and modulation of gaze on the connections.

Results: Bayesian model selection revealed a winning model, in which Vis showed bottom-up influence on mPFC, which in turn had direct top-down influences on alsn and TPJ and indirect top-down influence on Vis through TPJ; attending to gaze modulated the Vis-mPFC and mPFC-TPJ connections. Attending to gaze inhibited the bottom-up connection from Vis to mPFC in HC, and this inhibition was weakened in SZ.

Conclusions: These findings suggest that when determining the self-referential nature of social information, it is critical to suppress stimulus-driven processing and rely more on conceptually-driven cognition formulated from past experience. A reduced ability to do so may underlie the abnormalities observed in eye gaze perception in schizophrenia.
421. Discovering the “Functional Dysconnectome” in Schizophrenia: Dynamic Modulation of Brain Network Dysfunction during Learning and Visuo-Motor Processing

Valbhav Diwadkar
Wayne State University School of Medicine

Background: Structural brain networks are subject to dynamic functional demands (Park & Friston, 2013). As fMRI signals are sensitive to task-induced modulation (Logothetis, 2008), inducing functional dynamics can clarify aspects of the functional dysconnectome in schizophrenia (SCZ). We assessed the dysconnectome in two domains: a) Associative learning targeting frontal-striatal-hippocampal sub-networks and b) Basic visuo-motor integration targeting uni- and hetero-modal networks. Undirected functional connectivity (uFC) analysis of rs-fMRI signals in the time domain (Silverstein et al., 2016) was employed.

Methods: fMRI (3T) was collected in right-handed SCZ and controls (n=65 total) and typically modeled (SPM8). a) During learning, subjects encoded associations between object-location pairs for subsequent cued retrieval. b) During visuo-motor integration, subjects detected briefly presented probes (~1° in size appearing at a retinal eccentricity of ~7° along the horizontal meridian). Intra-subject correlation coefficients (Spearmann’s Rho or Pearson’s R) between sub-network pairs were computed, normalized (Fischer’s Z), and submitted for inter-group analyses (p<.05, Bonferroni).

Results: The functional dysconnectome was diffuse: a) For learning, the dPFC and the basal ganglia emerged as dysconnection hubs during encoding and retrieval, with reduced uFC with the hippocampus, and dorsal anterior cingulate (dACC). b) For visuo-motor integration the supplementary motor area, the dACC and the primary visual cortex emerged as dysconnection hubs, showing reduced uFC with multiple sensori-motor regions.

Conclusions: The functional dysconnectome in SCZ is dynamic, and by implication, structural disconnection exercises soft constraints on the functional dysconnectome. Understanding the functional dysconnectome in schizophrenia is a challenging instance of the complex dialectic between brain structure and function.

Supported By: Geram Research Foundation SCHL1969/1-1
Keywords: delusions, Working memory, effective connectivity, BOLD fMRI

423. NMDAR Antagonism via Ketamine Differentially Modulates Thalamic versus Hippocampal Functional Connectivity

Alan Anticevic1, Charlie Schleifer1, Vinod Sripari1, John Krystal2, John Murray1, Grega Repovs3, Gordon Xu4, Lisa Ji1, Youngsun Cho1, Nicole Santamauro1, Jennifer Foss-Feig2, Genevieve Yang1, Peter Morgan1, and Aleksandar Savic2

1Yale University, 2Yale University School of Medicine, 3University of Ljubljana, 4MSSM, 5University of Zagreb

Background: Disruption in brain-wide resting-state functional connectivity (rs-fcMRI) has been implicated in schizophrenia. This type of system-level disturbance has not yet been adequately mapped onto synaptic-level mechanisms, where pharmacological intervention occurs. Antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor is a prevailing pharmacological model for schizophrenia symptoms.

Methods: Using the NMDAR antagonism model, we examined effect of sub-anesthetic doses of ketamine on thalamic and hippocampal rs-fcMRI in healthy control subjects (HCS, n=27) relative to a placebo infusion. Neuroimaging data were acquired and processed in line with Human Connectome Project (HCP) methods. Across analyses, rs-fcMRI was computed between subjects with high-risk for psychosis. Recent imaging studies have identified abnormalities in prefrontal activation and in connectivity between frontal and parietal regions in different stages of psychosis. However, it still remains unexplored whether comparable functional changes are found in participants with subclinical levels of psychosis.

Results: We previously found in schizophrenia patients reduced WM-dependent effective connectivity from dorsolateral-prefrontal to parietal cortex compared to healthy controls. High PDI subjects were no impaired behaviorally but displayed increased local activation in dPFC. DCM analysis revealed reduced modulatory WM-dependent fronto-parietal connectivity and increased intrinsic parieto-frontal connectivity in subjects with high delusional ideation. In patients unsupervised classification revealed subgroups differing on negative symptoms.

Conclusions: Subjects with high delusional ideation showed an inefficient dPFC recruitment resulting from altered effective connectivity within the fronto-parietal network in accordance with a dimensional view of psychosis. Furthermore, our results suggest that parameters derived from generative models of neural activation during working memory can be feasible to identify mechanistically informed subgroups in schizophrenia patients.

Supported By: MH111177; NARSAD
Keywords: delusions, Working memory, effective connectivity, BOLD fMRI

422. Fronto-Parietal Effective Connectivity in Schizophrenia Patients and Participants with Subclinical Delusional Ideation

Florian Schlagenhau1, Yu Fukuda2, Teresa Katthagen2, Jakob Kaminski2, Lorenz Deserno1, and Andreas Heinz2

1Max Planck Institute, 2Department of Psychiatry, Chrité - Universitätsmedizin Berlin

Background: Impairment in working memory (WM) is one of the core cognitive dysfunctions in schizophrenia patients and subjects with high-risk for psychosis. Recent imaging studies have identified abnormalities in prefrontal activation and in connectivity between frontal and parietal regions in different stages of psychosis. However, it still remains unexplored whether comparable functional changes are found in participants with subclinical levels of psychosis.

Methods: We investigated schizophrenia patients and healthy controls with and without subclinical delusional ideations with functional MRI during numeric WM. Participants with high subclinical delusional ideations were identified using the Peters Delusion Inventory. Dynamical causal modeling (DCM) was used to assess effective connectivity between frontal and parietal brain regions during WM performance. Unsupervised classification was used to identify patient subgroups based on DCM parameters.

Results: We previously found in schizophrenia patients reduced WM-dependent effective connectivity from dorsolateral-prefrontal to parietal cortex compared to healthy controls. High PDI subjects were no impaired behaviorally but displayed increased local activation in dPFC. DCM analysis revealed reduced modulatory WM-dependent fronto-parietal connectivity and increased intrinsic parieto-frontal connectivity in subjects with high delusional ideation. In patients unsupervised classification revealed subgroups differing on negative symptoms.

Conclusions: Subjects with high delusional ideation showed an inefficient dPFC recruitment resulting from altered effective connectivity within the fronto-parietal network in accordance with a dimensional view of psychosis. Furthermore, our results suggest that parameters derived from generative models of neural activation during working memory can be feasible to identify mechanistically informed subgroups in schizophrenia patients.

Supported By: Geram Research Foundation SCHL1969/1-1
Keywords: delusions, Working memory, effective connectivity, BOLD fMRI
individual-specific anatomically-defined thalamic and hippocampal ROIs and all other gray matter vertices in CIFTI gray-ordinate space. Effects were examined using a 2x2 repeated measures ANOVA model with a factor of Infusion (ketamine vs. placebo) and Seed (thalamus vs. hippocampus). Brain-wide type I error protection was established through nonparametric permutation-based methods.

Results: We observed dissociable effects of NMDAR antagonism on thalamic versus hippocampal connectivity. NMDAR antagonism induced thalamo-sensory hyper-connectivity, but also reduced thalamo-cortical coupling with bilateral parietal and frontal association cortex, resembling prior observations in schizophrenia. Hippocampal effects exhibited the opposite pattern. Both effects were verified via an independent a priori large-scale network analysis, illustrating dissociable effects of ketamine on executive and sensory networks.

Conclusions: Collectively, these effects indicate that manipulating glutamatergic signaling via NMDAR antagonism can capture results observed in schizophrenia. This illustrates the potential utility of the ketamine model as a tool for refining clinically observable neuroimaging markers and informing future glutamatergic pharmacotherapies.

Supported By: NARSAD Independent Investigator Award; R01MH10859001; DP5OD01210905

Keywords: Schizophrenia, Ketamine, NMDA antagonists, BOLD fMRI, Functional connectivity

SYMPOSIUM
New Perspectives for Understanding Networks in Anxiety and Fear-Based Disorders
Friday, May 19, 2017 - 3:00 PM - 5:00 PM
Sapphire MN
Chair: Raul Andero

424. Genomic Mediators of PTSD in Blood and Brain
Nikolaos Daskalakis
Icahn School of Medicine at Mount Sinai

Background: Delineating the molecular basis of individual differences in the stress response is critical to understanding the pathophysiology of post-traumatic-stress disorder (PTSD).

Methods: We analyzed genome-wide expression of peripheral blood mononuclear cells (PBMCs) and functional neuroendocrinology and immunology plasma/serum data from a cross-sectional biomarker study with and without PTSD (n=83/group). In addition, gene expression in blood and brain (amygdala and hippocampus) were analyzed from a PTSD rat model, in which vulnerable and resilient phenotypes are identified according to the long-term behavioral response to predator scent stress (PSS).

Results: Differentially expressed (DE) genes were identified in association with PTSD. These DE genes were consistent with peripheral downregulation of glucocorticoid receptor (GR) signaling and upregulation of pro-inflammatory cytokine signaling. The gene expression differences in these pathways were validated in cultured PBMCs incubated in varying doses of dexamethasone (DEX). These findings were also replicated by the DE-signatures identified in rat blood and brain, in association with exposure-related individual differences. Gene co-expression networks were then identified. Among the most promising networks, there was a large (>100 genes) PTSD co-expression module showing a high level of dysregulation and high level of conservation in the blood and brain of PTSD-like rats. Functionally, this module is enriched with the genes related to innate immune response, and its eigengene expression associates deferentially with the PBMC lysozyme inhibition by DEX in the two groups.

Conclusions: GR-dependent immune pathways and networks are associated with trauma-related individual differences in blood and brain, and can be the basis of treatment for PTSD.

Supported By: DOD, NARSAD

Keywords: PTSD - Posttraumatic Stress Disorder, Glucocorticoids, gene expression profiling, Immune Activation, Brain

425. Immune Response to Trauma is Associate with Cognitive Functioning and Emotion Regulatory Dimensions Underlie the Development of Posttraumatic Stress Pathology: Evidence from a Naturalistic Emergency Room Study
Isaac Galatzer-Levy
NYU School of Medicine

Background: Traditional biological models of posttraumatic stress psychopathology have focused on simple direct relationships between biological factors and psychiatric diagnoses. In contrast, the developmental systems perspective proposes that the regulations of biological systems in response to extreme stress underlies dimensions of cognition and emotion regulation that ultimately influence individual's propensity to respond to the event in heterogeneous ways.

Methods: Results will be presented from the NYU/Bellevue Stress and Resilience, a longitudinal study of individual's recruited from the emergency room following an accident or injury. Immune and inflammatory response to the injury, reflected levels of neutrophils, lymphocytes, monocytes, eosinophils, and basophils are both directly associated with the development of depression and PTSD one month following admission to the emergency room and are associated with objective assessments of cognitive functioning (controlled attention, cognitive flexibility, inhibition, recall memory, and executive functioning) and emotion regulation (reflected in corrugator activity measured through facial electromyography; response time to fearful and angry faces).

Results: Together results indicate that the regulation of immune response to trauma may reflect regulatory processes that ultimately influence cognitive functioning and emotion regulation, ultimately influencing long term patterns of adaptation following trauma.

Conclusions: Distinct white blood cell responses point to molecular mechanisms that are worthy of further investigation in relation to cognition, emotion regulation, and ultimately the development of posttraumatic stress psychopathology.

Supported By: K01MH102415

Keywords: PTSD - Posttraumatic Stress Disorder, Inflammation, Autonomic Reactivity, Trajectories
426. PPM1F is Regulated by Stress and Associated with Anxiety and Depression

Aliza Wingo1, Adriana Lori2, Dennis Choi3, Tanja Jovanovic2, Kerry Ressler4, and Raul Andero1

1 Autonomous University of Barcelona, 2 Emory University, 3 Georgia State University, 4 McLean Hospital

Background: Stress is an important environmental modulator of brain activity. Exposure to stress or traumatic life experiences can increase the likelihood of developing depression or post-traumatic stress disorder (PTSD). Notably, PTSD is highly comorbid with depression among susceptible individuals.

Methods: For the mouse studies we used gene expression arrays in the amygdala and medial prefrontal cortex in response to immobilization to a board. Results were replicated by quantitative PCR (q-PCR). Moreover, behavior was measured using anxiety-like and depression-like tests. The human data was obtained analyzing blood RNA levels with beadChip arrays and DNA from saliva or blood with the Illumina’s HumanOmni1-Quad.

Results: The phosphatase PPM1F is regulated in the brain after exposure to traumatic stress in mouse models (N=4 per group for the arrays; N=8 to 12 per group for the q-PCR replication) and is associated with comorbid PTSD&Depression (Grady Trauma Project; GWAS, N=2361. RNA in blood levels, N=320) and chronic anxiety (N=316).

Conclusions: Taken together, our data suggest that a pathway involving PPM1F and CAMKII is involved in the mechanism of stress and trauma-related anxiety comorbid with depressive-like symptoms across species. PPM1F regulates CAMKII which is a cellular enzyme involved in many processes such as memory, stress, and the cardiovascular system. Thus, our stress-related findings may have implications not only in brain disorders but also in other fields of medicine in which PPM1F and CAMKII play key roles.

Supported By: KJR received support from the Howard Hughes Medical Institute, RA and KJR were supported by R21MH101492-01, KJR by R01MH071537 and R01MH096764, RA by a NARSAD Young Investigator Grant (22494), the Ramón y Cajal programme (RYC-2014-15784) and MOCINN SAFSAF2016-76565. APW was supported by the Department of Veterans Affairs Career Development Award IK2CX008601 and the NARSAD Young Investigator Award. TJ has support from NARSAD and R01MH100122.

Keywords: Amygdala, PTSD depression, stress, Prefrontal Cortex, Mechanisms

427. Predictors of Resilience to Deployment Stress: Prospective Observations

Murray Stein1, Chia-Yen Chen2, Ronald Kessler3, Sonia Jain4, Joel Gelernter1, Jordan Smoller2, and Robert Ursano3

1 University of California San Diego, 2 Massachusetts General Hospital, 3 Harvard School of Medicine, 4 Yale University, 5 Uniformed Services University

Background: There is great interest in factors that can promote resilience to the serious experiential stressors. This interest is particularly relevant to the military, where traumatic stressors such as deployment to combat situations may have a deleterious effect on the health of warfighters.

Methods: The New Soldier Study (NSS) of the Army Study to Assess Risk and Resilience to Servicemembers (Army STARRS) surveyed approximately 38,000 US Army recruits during Basic Combat Training. The Pre-Post Deployment Study (PPDS) of Army STARRS surveyed approximately 8,000 soldiers within 3 Brigade Combat Teams 4-6 weeks prior to their deployment to Afghanistan (T0), and then prospectively reassessed them upon their redeployment to the US (T1), two months later (T2), and six months later (T3). Genomewide association analysis (GWAS) was conducted using standard methods and related to the phenotypes of (1) a 5-item measure of self-reported resilience, and (2) prospective resilience as defined by good mental health outcomes post-deployment in PPDS.

Results: Childhood maltreatment was found to be a robust predictor of low self-reported resilience. Using GCTA to estimate SNP-based heritability, self-reported resilience was found to be significantly heritable ($h^2 = 0.135, se = 0.030, p = 2.02e-7) in the European American (EA) sample (N=11,492). A meta-analysis across cohorts of GWAS results from the EA subjects revealed a genomewide significant locus (4 SNPs in LD; top SNP: rs4260523, $p = 5.65e-09$) on Chr 4 just upstream from DCLK2 (Doublecortin-Like Kinase 2), involved in hippocampal organization.

Conclusions: This study of US Army soldiers revealed experiential and genetic contributions to self-reported resilience.

Supported By: Army STARRS was sponsored by the Department of the Army and funded under cooperative agreement number U01MH087981 with the U.S. Department of Health and Human Services, National Institutes of Health, and National Institute of Mental Health (NIH/NIMH).

Keywords: Resilience, Posttraumatic Stress Disorder, combat stress, genome-wide association study, childhood maltreatment

SYMPOSIUM
Neural Substrates of Auditory Plasticity
Friday, May 19, 2017 - 3:00 PM - 5:00 PM
Sapphire 400 AB
Chair: Joshua Kantrowitz
Co-Chair: Sophia Vinogradov

428. Neurophysiological Mechanisms of Cortical Learning Plasticity Impairments in Schizophrenia and Modulation by the N-Methyl-D-Aspartate Type Glutamate Receptor Agonist D-Serine

Joshua Kantrowitz1, Michael Epstein2, Odeta Beggs3, Stephanie Roghrig3, Jonathan Lehrfeld3, Nadine Revheim3, Nayla Lehrfeld3, Jacob Reep3, Emily Parker3, Gail Silipo3, Merav Ahissar4, and Daniel Javitt1

1 Columbia University/Nathan Kline Institute, 2 City University, 3 Nathan Kline Institute, 4 Hebrew University of Jerusalem

Friday Abstracts
**Background:** Schizophrenia is associated with deficits in cortical plasticity that affect sensory brain regions and lead to impaired cognitive performance. Here we examined underlying neural mechanisms of auditory learning plasticity and plasticity deficits using combined behavioral and neurophysiological assessment, along with neuropharmacological manipulation targeted at the N-methyl-D-aspartate type glutamate receptor (NMDAR).

**Methods:** Cortical plasticity was assessed in a cohort of 40 schizophrenia/ schizoaffective patients (SzP) relative to 42 healthy controls (HC) using a fixed reference tone auditory learning plasticity task. In a second cohort (n=21 SzP/13 HC), event-related potential (ERP) and event-related spectral perturbation (ERSP) time-frequency measures of auditory dysfunction were assessed during administration of the NMDAR agonist d-serine. Mismatch negativity (MMN) was used as a functional read-out of auditory-level function.

**Results:** SzP showed significantly reduced auditory plasticity vs. HC (p<0.001) that correlated with measures of cognitive, occupational, and social dysfunction. In ERP/ERSP time-frequency analyses, patients showed highly significant reductions in sensory N1 that reflected underlying impairments in responses (p<0.001), along with reduced and -power modulation during retention and motor-preparation intervals. Repeated administration of d-serine led to intercorrelated improvements in 1) auditory plasticity (p<0.001), 2) -frequency response (p<0.05), and 3) MMN generation to trained vs. untrained tones (p<0.02).

**Conclusions:** SzP show highly significant deficits in auditory plasticity that contribute to cognitive, occupational and social dysfunction. d-Serine studies suggest first that NMDAR dysfunction may contribute to underlying cortical plasticity deficits and, second, that repeated NMDAR agonist administration may enhance cortical plasticity in Sz.

**Supported By:** National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 RR024156 and the Dr. Joseph E. And Lillian Pisetsky Young Investigator Award for Clinical Research in Serious Mental Illness to JTK and by the NIH grants (P50 MH086385, R01 MH049334) to DCJ.

**Keywords:** Glutamate, NMDAR, Auditory, Schizophrenia, Neuroplasticity

**429. Increased Serum Levels of the NMDA Receptor Co-Agonist D-Serine Are Associated with Improved Cognition after Training in Schizophrenia**

**Sophia Vinogradov, Melissa Fisher, and Rogerio Panizzutti**

1University of Minnesota Medical School, 2University of Minnesota Medical Center, 3Universidade Federal do Rio de Janeiro, Instituto de Ciencias Biomedicas

**Background:** Cognitive training of auditory processing in schizophrenia induces significant improvement in cognition and plasticity in cortical activation patterns, but the biological mechanisms underlying these changes are unknown. In animals, intensive cognitive activity increases brain levels of the NMDA-receptor co-agonist D-serine, a molecular system which plays a key role in learning-induced neuroplasticity and which may be hypoactive in schizophrenia. We investigated whether training-induces cognitive gains were associated with increases in serum D-serine levels.

**Methods:** Ninety clinically stable participants with schizophrenia and 53 healthy controls were assessed on baseline serum D-serine, L-serine, and glycine. Schizophrenia subjects performed neurocognitive assessments and were assigned to 50 hours (10 weeks) of either targeted cognitive training of auditory processing (N=47) or to a computer games control condition (N=43). After the intervention, neurocognitive assessments and serum amino acid analyses were repeated.

**Results:** At baseline, the mean serum D-serine level was significantly lower in schizophrenia participants than healthy controls, while serum glycine levels were significantly higher. There were no significant changes in these measures at a group level after the intervention. However, in auditory training subjects, increased serum D-serine levels after training were significantly and positively correlated with improvements in global cognition (r=0.41, p=0.005) and verbal learning/memory (r=0.54, p<0.0001). No such associations were found in the computer games control group, nor were found for glycine.

**Conclusions:** D-serine may be involved in the neurophysiologic changes induced by intensive cognitive training of auditory systems in schizophrenia. Pharmacologic strategies that target D-serine co-agonism of NMDA-receptor functioning may enhance the behavioral effects of cognitive training.

**Keywords:** NMDA Receptor, Cognitive Training, Schizophrenia, Neuroplasticity

**430. Leveraging Auditory Information Processing Neuroplasticity towards Therapeutic Development in Schizophrenia**

**Neal Swerdlow, Savita Bhakta, Michael Thomas, Yash Joshi, Wen Zhang, Jo Talledo, and Gregory Light**

University of California, San Diego

**Background:** Laboratory measures can quantify auditory information processing (AIP), including neurophysiological measures of lead- or deviant-sound effects on auditory evoked responses, and neurophysiological and behavioral responses to masked or degraded simple and complex sounds. Evidence suggests that impaired early AIP is a root cause of neurocognitive and functional impairment in schizophrenia; interventions that enhance early AIP in schizophrenia patients are thus rational targets for therapeutics.

**Methods:** We tested the use of AIP measures to develop strategies for enhancing neurocognition and hence function in schizophrenia patients, via two experimental medicine studies in antipsychotic-mediated schizophrenia patients and healthy subjects (HS).

**Results:** One study tested the impact of the NMDA antagonist, memantine (20 mg) on measures of early AIP. Memantine significantly increased AIP measures: prepulse inhibition, mismatch negativity and gamma band synchronization (phase locking and evoked power) (p’s<0.04-0.0015). A second study tested the effects of amphetamine (10 mg) on auditory processing speed (APS) during 1-h of “Sound Sweeps” Targeted Cognitive Training. APS learning (post- vs pre-training) was enhanced by amphetamine (p<0.002), and this learning was sustained for at
least 1 week. Effects of both memantine and amphetamine were evident in patients and HS, suggesting that drugs acted on healthy substrates with substantial neuroplasticity.

**Conclusions:** Evidence connecting AIP, neurocognition and function opens new avenues for studies of novel therapeutic approaches to schizophrenia. We report two experimental medicine approaches that may: 1) demonstrate substantial neuroplasticity in AIP mechanisms in schizophrenia; 2) identify biomarkers for “drug-sensitive” individuals; and 3) explicate neurochemical mechanisms that link AIP to outcome in schizophrenia patients.

**Supported By:** NARSAD, VA-MIRECC

**Keywords:** amphetamine, memantine, Schizophrenia, auditory processing, cognitive training

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**SYMPOSIUM**

**The Neurobiology of Conduct Disorder:**

**Understanding the Impact of Sex Differences in the FemNat-CD European Consortium**

Friday, May 19, 2017 - 3:00 PM - 5:00 PM

Sapphire 410 AB

Chair: Christine Freitag

Co-Chair: Stephane De Brito

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**431. The Effect of Bilateral Transcranial Direct Current Stimulation on Tone Matching Task Performance and Mismatch Negativity in Schizophrenia**

Walter Dunn1, Jonathan K. Wynn2, Yuri Rassovsky3, Allan Wu4, Marco Iacoboni5, Gerhard Hellermann6, and Michael F. Green2

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**Background:** Schizophrenia (SZ) is characterized by auditory processing deficits which are treatment targets as they contribute to higher order cognitive dysfunction and are correlated with functional outcomes. Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation method that modulates cortical activity in a polarity-dependent manner. In two separate studies, we examined the effect of tDCS on a behavioral measure (Tone Matching Task, TMT) and a neural measure (mismatch negativity, MMN) of early auditory processing in people with SZ.

**Methods:** Study 1: In a parallel group study with random assignment, anodal, cathodal, or sham tDCS stimulation was delivered bi-frontally at Fp1 and Fp2. MMN was assessed at baseline and post-stimulation. Study 2: In a within-subject cross-over study, anodal, cathodal and sham tDCS were delivered through two electrodes bi-temporally at C5 and C6. TMT and MMN was assessed after each stimulation.

**Results:** Study 1: Comparing baseline and post-stimulation amplitudes separately for each condition revealed a significant decrease in MMN amplitude for anodal stimulation, t10 = 3.06, p < 0.05, (Cohen’s d = 0.95), and no other effects. Study 2: For TMT, there was a significant main effect of tDCS condition (F2,4625 = 3.58, p < 0.03) with cathodal stimulation significantly improving TMT performance vs sham condition (p < 0.01).

**Conclusions:** tDCS stimulation of prefrontal vs temporal regions in subjects with schizophrenia yielded different patterns in measures of early auditory processing in a polarity-dependent manner. These results suggest that early sensory network deficits in schizophrenia can be modulated by

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**432. Sex Differences in the Relationship between Conduct Disorder and Cortical Structure in Adolescents**

Areti Smaragdi2, Harriet Cornwell2, Nicola Toschi3, Karen Gonzalez2, Roberta Riccilli2, Amy Wells2, Ignazio Puzzo2, Roberta Clanton5, Rosalind Baker4, Jack Rogers2, Anka Bernhard6, Anne Martellini6, Christine Freitag7, Nora Raschle8, Christina Stadler9, Gregor Kohls10, Sarah Baumann11, Kerstin Konrad12, Edmund Sonuga-Barke6, Stephane de Brito13, and Graeme Fairchild1

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**Background:** Despite evidence that the clinical phenotype of Conduct Disorder (CD) differs between males and females, no imaging studies have included sufficient female participants to investigate sex differences in the relationship between CD and cortical structure.

**Methods:** Surface-based morphometry methods, implemented in FreeSurfer, were used to test for main effects of diagnosis and sex, and sex-by-diagnosis interactions across cortical thickness, surface area and gyriﬁcation, in a sample of 48 female and 48 male adolescents with CD and 104 sex-, age- and pubertal status-matched controls (aged 14-18 years). Subcortical volumes were computed using FreeSurfer’s automated segmentation tool. Participants were assessed for CD and comorbid disorders using the K-SADS-PL.
Results: CD was associated with cortical thinning and increased gyrification in ventromedial prefrontal cortex in both males and females. Several sex-by-diagnosis interactions were also observed: Males with CD showed lower, and females with CD showed higher, supramarginal gyrus cortical thickness, relative to their respective control groups. Males with CD showed higher superior frontal gyrus surface area and gyrification relative to male controls, whereas the opposite pattern was seen in females. These results remained significant when controlling for ADHD comorbidity. There were no diagnosis effects or sex-by-diagnosis interactions in subcortical volumes.

Conclusions: This study provides the first robust evidence for sex differences in the relationship between CD and brain structure, suggesting the pathophysiological basis of CD may be partly sex-dependent. These results highlight the need to consider males and females separately in future neuroimaging studies and the possibility that males and females may require different treatments.

Supported By: This study was funded by the European Union's FP7 Programme for research, technological development and demonstration under Grant Agreement no 602407 (FemNAT-CD).

Keywords: Conduct Disorder, Antisocial Behavior, Cortical Thickness, Structural MRI, Sex differences

433. Investigation of White Matter Microstructure Differences in Male and Female Youths with Conduct Disorder in the FemNAT-CD Study

Jack Rogers1, Karen Gonzalez2, Rosalind Baker3, Roberta Clanton4, Ruth Pauli3, Areti Smaragdi4, Justina Sidlauskaitė5, Roberta Riccelli6, Kerstin Konrad6, Gregor Kohls6, Nora Raschle7, Willeke Menks7, Christina Stadler8, Graeme Fairchild9, and Stepance de Brito1

1University of Birmingham, UK, 2Department of Psychology, University of Southampton, 3School of Psychology, University of Birmingham, UK, 4Department of Psychology, University of Southampton, UK, 5University Hospital, RWTH Aachen, Germany, 6University Hospital RWTH Aachen, 7Department of Child and Adolescent Psychiatry, Psychiatric University Clinics and University of Basel, Switzerland, 8Basel University, Switzerland, 9Department of Psychology, University of Bath

Background: Atypical brain structure in youths with conduct disorder (CD) has been observed in regions central to emotional processing and regulation. Diffusion tensor imaging (DTI) measures changes in the microstructure of white matter tracts in the brain, with fractional anisotropy (FA) one indirect measure of quantifying these structural changes. However, evidence for abnormalities in white matter integrity in youths with CD has been inconsistent and to-date only two studies with small samples have examined sex differences.

Methods: DTI data from four sites collected as part of the FemNAT-CD study comprised of male CD (N=74; M age=15) and female CD youths (N=63; M age=15.3) and age-matched typically developing (TD) male (N=74; M age=14.42) and female (N=116; M age=14.33) youths. DTI data were analysed using tract-based spatial statistics with FA maps generated as indicators of white matter microstructural integrity changes between youths with CD and TD youths.

Results: Analysis revealed significantly increased FA in the corpus callosum (forceps minor) bilaterally for CD compared to TD youths (p < .05 FWE-corrected) across the mean FA skeleton. Region of interest analysis revealed increased FA in the uncinate fasciculus (UF) for male CD youths compared to male TD youths.

Conclusions: Connectivity abnormalities of the anterior corpus callosum are linked to interhemispheric inhibition and behaviours such as impulsivity and aggression, typically observed in CD. Differences in FA observed in the UF may also help inform pathological differences in males vs. females with CD. Measures of local diffusion, the influence of personality traits, comorbidities, and environmental risk factors will also be examined.

Supported By: The European Commission’s Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 602407 (FemNAT-CD) (http://www.femnat-cd.eu)

Keywords: Conduct Disorder, white matter integrity, Diffusion Tensor Imaging (DTI), Sex differences, Tract-Based-Spatial-Statistics (TBSS)

434. Sex Differences in Emotional Dysfunction in Conduct Disorder (CD)

Kerstin Konrad, Gregor Kohls, Sarah Baumann, Caroline Biskup, and Beate Herpertz-Dahlmann

University Hospital RWTH Aachen

Background: Converging evidence suggests that deficits in emotion recognition, emotion learning, and emotion regulation may contribute to conduct problems, however, still little is known about sex-specific profiles of emotion dysfunction in youth with Conduct Disorder (CD).

Methods: As part of a European multi-site study (FemNAT-CD), emotion recognition, emotion learning and emotion regulation were assessed in subjects (aged 9-18 y) with and without CD (N= 1265) using a battery of computerized tasks. Repeated-measures ANCOVAs with age, IQ and site as covariates were run, followed by post-hoc contrasts with Bonferroni corrections.

Results: CD cases differed from controls with respect to empathic abilities, reactive-proactive aggressive behaviors and callous-unemotional and psychopathic traits. Significant group x sex interaction effects were found for callous-unemotional and psychopathic traits in which case-control differences were larger in females compared to boys. In addition, we found impaired emotion recognition across all basic facial emotions, impaired cognitive and emotional control as well as deficient reward-based learning in CD subjects compared to controls, with group x sex differences being most pronounced within the reward-based learning task. While girls showed better emotion recognition abilities independent of group, only boys with CD were particularly insensitive to punishment cues in the reward-based learning task.

Conclusions: Assessing emotional functions by standardized computerized tasks can provide important quantitative measures of cognitive/affective processing and might thus
help to unravel specific associations between clinical symptoms and emotional impairments in CD. This might contribute to delineate distinct (and possibly sex-specific) developmental pathways to CD which are relevant for developing more individualized treatment options.

Supported By: EU-FP7: Grant Agreement no 602407 (FemNAT-CD)

Keywords: emotion dysfunction, computerized tasks, Conduct Disorder, sex differences

435. Cortisol, Sex Hormone and Social Neuropeptide Related Correlates of Female Adolescent Conduct Disorder

Christine Freitag1, Kerstin Konrad2, Christina Stadler3, Graeme Fairchild4, Stephane de Brito5, Arne Popma6, Inga Neumann7, Aranzazu Fernandes Rivas8, and Anka Bernhard9

1University Hospital Frankfurt, Goethe University, 2University Hospital, RWTH Aachen, 3Basel University, 4University of Bath, 5University of Birmingham, 6University of Amsterdam, 7University of Regensburg, 8University of Bilbao, 9University Hospital Frankfurt

Background: Previous studies have implicated the stress and sex hormone system in CD aetiology in males with CD. The role of hormones implicated in social interaction, such as oxytocin and vasopressin, has rarely been studied despite findings from animal studies indicating a role of these neuropeptides in aggressive behaviour, and the interaction of the stress hormone system with oxytocin. The aim of the current study is compare cortisol, testosterone, estrogen and progesterone levels female and male in adolescents with CD, study their correlation with social neuropeptide level, and explore a neuroendocrinological risk pattern for adolescent female conduct disorder.

Methods: As part of a European multi-site study (FemNAT-CD), data from 4 x N=100 male and female individuals with CD and typically developing age and puberty status matched controls are analysed with regard to saliva derived basal cortisol, sex hormone and social neuropeptide level. Specific neuroendocrinological classes are explored by cluster analysis. Group comparisons are done by ANCOVA. Correlation analysis with CU traits and aggressive behaviour scores are done by linear modelling.

Results: First results show equal basal cortisol levels in CD and typically developing controls without differences between males and females. In contrast, main effects of sex and CD were observed for testosterone, which was positively associated with CD and being male. Additional results are pending.

Conclusions: Basal saliva hormone and neuropeptide measures are easily clinically obtained and may be used as markers for differential CD subtypes. The results of this study indicate a differential underlying neurobiology of CD in female compared to male CD.

Supported By: EU FP7 FemNAT-CD; Grant no 602407

Keywords: Conduct Disorder, females, adolescents, neuroendocrinology, neuropeptides

436. The t11:11 Translocation is Linked to Psychiatric Disorder, Glutamate, Cortical Structure/Function and Connectivity

Stephen Lawrie

University of Edinburgh

Background: Rare genetic variants of large effect can help elucidate the pathophysiology of brain disorders. The so-called DISC1 variant has been associated with schizophrenia and other disorders, whereas common variation in DISC1 does not appear to be a risk factor for psychiatric disorder.

Methods: This presentation expands the clinical and genetic analyses of a family with a (1:11)(q42;q14.3) translocation multiply affected by major psychiatric illness and examines the effect of the translocation on the structure and function of the brain through multi-modal neuroimaging.

Results: The translocation showed significant linkage with a clinical phenotype that included psychotic disorders (LOD=3.3); only affective disorders (bipolar disorder and recurrent major depression) (LOD=3.5); or all such cases of major mental illness (LOD=6.1). A maximum LOD score was obtained if the phenotype is further extended to include three cases with cyclothymia (LOD=7.9). Translocation carriers showed significantly increased activation in the caudate nucleus on increasing verbal working memory load, as well as reductions in the right dorsolateral prefrontal cortex glutamate concentrations. Translocation carriers showed reduced cortical thickness in the left temporal lobe, and reduced FA in the corpus callosum, which correlated with positive psychotic symptom severity. Differences were also evident in functional connectivity on fMRI and DTI connectomic measures.

Conclusions: These findings confirm that the t(1:11) translocation is associated with a significantly increased risk of major psychiatric disorder and suggest it brings a general vulnerability to psychopathology through altered cortical structure and function, and decreased glutamate levels.

Supported By: Translational Medical Research Consortium

Keywords: Imaging genetics, Psychoses, Affective Disorders, psychiatric disorders

437. Modeling Schizophrenia in Human Induced Pluripotent Stem Cells (hiPSCs): Phenotypic Differences in Patients with Mutations in NDE1

Mandy Johnstone1, Navneet Vasistha1, Heather Whalley1, Karen Burr1, David St. Clair2, Douglas Blackwood1, Eve Johnstone1, Stephen Lawrie1, Andrew McIntosh1, and Siddharthan Chandran1

1University of Edinburgh, 2University of Aberdeen
Background: Schizophrenia is a major psychiatric disorder with strong evidence of genetic risk factors. Large-scale studies have shown that structural genomic variation, in the form of copy number variants (CNVs), accounts for a significant portion of schizophrenia risk, including both sporadic and familial CNVs – most relatively rare, but of moderate to high penetrance. CNVs associated with schizophrenia, specifically those occurring in the disrupted in schizophrenia 1 (DISC1)-interactor, Nuclear distribution factor E-homolog 1 gene (NDE1), are proposed to exert their effect by converging on glutamate signaling pathways regulating synaptic plasticity. Furthermore, NDE1 is part of the LIS1/cytoplasmic dynein complex and as such participates in regulation of cell proliferation, migration and intercellular transport.

Methods: We have generated a platform of hiPSCs from patients with schizophrenia and neurodevelopmental disorders who are known to have CNVs affecting NDE1. We have undertaken comparative studies between mutant and control cell lines including proliferation of neural precursors, morphology of differentiated neurons, neuronal expression, and signaling pathways. In parallel we have studied the effects of NDE1 mutations on developmental pathways in ‘cerebral organoids’, a three-dimensional tissue culture of hiPSC that mimics early stages of human cortical development.

Results: Brain imaging of patients carrying NDE1 CNV showed reduced brain volume. IPSC-derived brain organoids from these patients were smaller and showed reduced neuronal progenitor cell proliferation. This was associated with deficits in key intracellular signaling pathways.

Conclusions: Our data shows that NDE1 plays an important role in the development of the human cerebral cortex and mutations in NDE1 result in abnormalities in corticogenesis.

Supported By: R42838; Wellcome Trust

Keywords: Schizophrenia, Neurodevelopmental disorders, hiPSC, Cerebral organoids, DISC1 interactome

438. Amyloidogenic DISC1: Role for Psychiatric Manifestation in Neurodegenerative Disorders
Koko Ishizuka1, Motomasa Tanaka2, Miles Houslay3, and Akira Sawa4
1Department of Psychiatry, Johns Hopkins University School of Medicine, 2RIKEN Brain Science Institute, 3Institute of Pharmaceutical Sciences, King’s College London, 4Johns Hopkins University

Background: Molecular mechanisms for non-motor symptoms such as psychiatric manifestations in Huntington’s disease (HD) remain elusive. Deficits of cAMP-degrading phosphodiesterase-4 (PDE4) have been reported in HD, and one of the critical interactors of PDE4 is a scaffold protein DISC1 that has amyloidogenic nature. Here we address a novel molecular mechanism involving DISC1-PDE4 interactions for psychiatric manifestation in neurodegenerative disorders, by using HD as a model system.

Methods: PDE4 enzymatic activity was measured by a fluorescence polarization assay. Biochemical, biophysical, and immunohistochemical approaches were applied to study protein interactions of PDE4, DISC1, and Huntington (Htt). Behavioral assays were conducted to study both motor and non-motor symptoms. Molecular intervention was made by stereotaxic injection of AAV into the striatum of the HD mouse model R6/2.

Results: We demonstrate that Htt forms a ternary protein complex with DISC1 and PDE4, which regulates PDE4 activity. The pathogenic sequestration of amyloidogenic DISC1 into mutant Htt aggregates by cross-seeding is observed in the brains of HD patients and those of the R6/2 model. Consequently, the R6/2 model shows a PDE4 fraction becoming out of physiological control by DISC1, aberrantly increasing the activity of PDE4. Importantly, exogenous expression of DISC1 that binds to PDE4, but not mutant Htt, normalizes PDE4 activity and ameliorates reduced motivation for pleasure in the R6/2 model.

Conclusions: We propose that cross-seeding of mutant Htt and DISC1 and resultant changes in PDE4 may underlie the pathology in a specific subset of psychiatric manifestations of HD.

Keywords: DISC1 interactome, PDE4, Huntington, Motivation for pleasure

439. Role for DISC1 in Sensorimotor Gating: Its Impact on Corticostriatal Transport of BDNF
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1Centre for Addiction and Mental Health, University of Toronto, 2Duke University Medical Center, 3CHU Grenoble Alpes, France, 4Johns Hopkins University

Background: Sensorimotor gating is a crucial behavioral endophenotype for higher brain function. It is measured by prepulse inhibition (PPI), which is disturbed in multiple neuropsychiatric conditions. It is important to elucidate a mechanism that accounts for sensorimotor gating at both molecular and circuity levels.

Methods: We used a Disc1 haploinsufficiency model (Disc1 locus impairment mice). We studied the model with behavioral tests including PPI and anatomical assessment by ex vivo MRI. We performed in vivo electrophysiological recordings in the prefrontal cortex and the dorsal medial striatum during PPI testing. We used also optogenetics to stimulate the prefrontal cortex. We measured the levels of Bdnf by ELISA. Molecular intervention towards rescue of behavioral deficits was made by stereotaxic injection of AAV-BDNF to the striatum or systemic administration of lithium.

Results: There were anatomical deficits in the striatum and PPI abnormalities in the Disc1 model. Gating function of the prefrontal cortex on the striatal response during PPI was disturbed, although neural response inside the prefrontal cortex was intact. Thus, we focused on a molecular mechanism of corticostriatal signaling. We found that corticostriatal trafficking of Bdnf was disturbed in the Disc1 mice. We further elucidated that the protein interaction of DISC1 with phospho-Huntingtinx specifically at Ser-421 is the key driver for the proper trafficking of Bdnf. Accordingly, stereotaxic injection of AAV-BDNF to the striatum or systemic administration of lithium ameliorated the deficits in the Disc1 mice.

Conclusions: We provide a novel mechanism for sensorimotor gating, mediated by DISC1 in the corticostriatal neurons together with its interactors.
440. Defining Trans-Diagnostic Psychiatric Traits Using Reinforcement Learning Models in Large Online Samples

Claire Gillan
New York University

**Background:** Attempts to link brain data, or behavioral assays thereof, to discrete diagnostic categories have been met with limited success. One alternative approach to understanding the neurobiological substrates of psychopathology is to adopt a more data-driven approach; to use behavioral assays of brain data (i.e. cognitive tasks) to determine which symptoms cluster together in the most biologically relevant manner.

**Methods:** Here, we describe data collected from three independent studies, involving close to 3000 research participants in total, which were collected entirely via the Internet. Subjects completed behavioral tasks that measure discrete aspects of reinforcement learning (RL), linked to prefrontal and striatal function respectively and also completed self-report questionnaires that assess symptoms characteristic of a range of DSM disorders. Individual differences in these dissociable aspects of RL were then related to self-report psychopathology in a data-driven way with the goal of revealing trans-diagnostic psychiatric dimensions that hold biological plausibility.

**Results:** We found evidence suggesting that the compulsive symptoms that many disorders share are linked to deficits in goal-directed ('model-based') RL. These data will be discussed and contrasted with results for slowly acquired associative learning, which has been previously linked to striatal dopamine.

**Conclusions:** A key goal of biological psychiatry is to define brain mechanisms that cause psychiatric symptoms – these data make the case that moving beyond diagnostic categories may be a fruitful way to progress in this regard.

**Supported By:** Wellcome Trust 101521/Z/12/Z

**Keywords:** Computational Psychiatry, Compulsivity, Model-based and model-free decisions, Depression, Anxiety

441. New Learning or Unlearning: Computational Heterogeneity in Extinction Predicts the Recovery of Threat Responses

Catherine Hartley
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**Background:** Anxiety disorders are characterized by persistent and debilitating fear. Exposure therapies, based on the principles of extinction learning, are effective for many. However, for some, extinguished threat responses reemerge, a phenomenon that compromises the efficacy of such therapies. Here, we propose that this heterogeneity might stem from qualitative individual differences in the nature of extinction learning that can be captured by a computational process model.

**Methods:** We fit to participants' physiological conditioning data a model (Gershman et al., 2010) positing that learners attempt to segment their experience into "states" or "latent causes" that capture regularity in the configuration of observed stimuli (cue and reinforcement). The model can distinguish those who appear to cluster CS and US observations during threat learning and extinction into a single state, effectively updating the original threat association, or into two states reflecting separate threat or safety associations, permitting extinguished responses to reemerge.

**Results:** Although spontaneous recovery of extinguished threat responses is a well-documented phenomenon at the group level, there was substantial heterogeneity in our sample. The model distinguished those whose data was best fit by a one-state unlearning-like representation from those who appeared to infer distinct threat and safety states. Strikingly, only the group of "two-state" learners exhibited spontaneous recovery the following day.

**Conclusions:** Qualitative variation in extinction learning may have important implications for understanding vulnerability and resilience to fear-related psychiatric disorders. Moreover, developmental changes in extinction learning may provide insight into the typical onset and peak prevalence of anxiety in adolescence.

**Keywords:** Extinction Learning and Recall, Computational Modeling

442. Methylphenidate Optimizes the Rate of Error-Driven Learning in Healthy Males

Martin Paulus¹ and Jonathon Howlett²
¹Laureate Institute for Brain Research, ²University of California San Diego

**Background:** Adaptive behavior relies on the ability to make adjustments in the face of unexpected outcomes, a process that is dysfunctional in anxious individuals. This process, known as error-driven learning, is described by the classic Rescorla-Wagner (RW) model. The learning rate is a key parameter and determines the degree of modification in beliefs (and consequently behavior) after a given prediction error. This investigation examined whether modulation of the dopamine and norepinephrine system affects the learning rate in this context.

**Methods:** 20 healthy male subjects (age 25.9 +/- 6.6 years) performed a probabilistic learning task during randomized in double-blind placebo controlled sessions of placebo or methylphenidate (40 mg). The task consisted of 3 blocks with 60 trials each. The target stimulus appeared in the three locations according to a probability distribution with frequency 1:3:9.

**Results:** Across subjects in session 1, behavioral learning rate was positively correlated with performance (R=0.75, p<0.001).
Within session 1, behavioral learning rate explained an estimated 73% of the performance difference between subjects receiving MPH and placebo. We further investigated group differences by estimating a standard RW learning model with two free parameters per subject, per block (learning rate $\eta$ and inverse temperature parameter $\beta$). Model accuracy in predicting individual decisions was high (0.76). When averaged across blocks, MPH subjects had significantly higher RW learning rate $\eta$ than PLB in session 1 ($p=0.048$).

**Conclusions:** Overall, the current study suggests a new, NE-mediated treatment mechanism targeting deficits in the adaptation of learning rate to environmental characteristics.

**Keywords:** Methylphenidate, Computational Modeling, Anxiety, Learning, Pharmacology

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**443. Characterisation of a Computationally Defined Treatment Target for Anxiety and Depression**

Michael Browning and Erdem Pulcu

University of Oxford

**Background:** Preferential learning from negative at the expense of positive events, has been causally linked to anxiety and depression. This suggests that interventions which target such negative learning bias may reduce symptoms of the illness, although the best way to achieve this is not clear. Recent computational work suggests that people preferentially learn from outcomes with high information content (i.e. which improve prediction of the future), and that central norepinephrine acts to report the information content of the outcomes. We tested whether it was possible to manipulate learning bias and associated central norepinephrine activity by controlling the information content of positive and negative events in a computer based task.

**Methods:** In the study 30 non-clinical participants completed a learning task in which the information content of positive and negative outcomes (wins and losses) was independently manipulated by controlling their volatility. Pupillometry data was collected to assess central norepinephrine activity. A simple computational model was used to estimate learning rate for wins and losses.

**Results:** Participants demonstrated a significant increase in learning rate to the particular event (wins or losses) which carried more information ($F=52$, $p<0.01$). Activity of the central norephipheric system was similarly modified by the intervention ($p<0.01$).

**Conclusions:** These results indicate that people maintain separate estimates of the information content of positive and negative outcomes, and these estimates may be targeted by a simple cognitive intervention. In an ongoing randomised clinical study the effects of this intervention on symptoms of depression is being tested.

**Supported By:** MRC MR/N008103/1

**Keywords:** Depression, Computational Psychiatry, Norepinephrine

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**SYMPOSIUM**

**Multimodal Imaging of Electroconvulsive Therapy at the Human System Level**

Friday, May 19, 2017 - 3:00 PM - 5:00 PM

Aqua D

Chair: Indira Tendolkar

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**444. Global and Regional Perfusion MRI Predicts Antidepressant Response to ECT**

Katherine Narr1, Amber Leaver2, Megha Vasavada2, Shantanu Joshi2, Roger Woods2, and Randall Espinoza2

1UCLA Brain Research Institute, 2UCLA

**Background:** Converging evidence suggests that electroconvulsive therapy (ECT) induces neuroplasticity in specific cortico-limbic networks in patients with recurrent depression. Here, we measured cerebral blood flow (CBF) with arterial spin-labeled (ASL) magnetic resonance imaging (MRI) to assess neurofunctional predictors and correlates clinical response to ECT.

**Methods:** Patients ($n=42$) were assessed before ECT, after 2 treatments, and after index (2-4 weeks later). Age- and sex-matched controls were scanned twice ($n=33$), 2-4 weeks apart. Linear mixed-effects models assessed changes in global and voxelwise CBF in responders and non-responders, controlling for age, global CBF, gray-matter content, treatment parameters, and multiple comparisons as appropriate.

**Results:** After ECT index, CBF increased in the right anterior hippocampus. The position and extent of this effect differed between responders and nonresponders, such that responders exhibited a more focal and slightly more posterior regional increase in hippocampal CBF than nonresponders. Positive antidepressant response was also associated with increased CBF in the left dorsal thalamus, and decreased CBF in right temporoparietal cortex. Lower global CBF prior to ECT, and increased CBF after two treatments, both predicted positive antidepressant response.

**Conclusions:** Our data support a growing literature indicating that ECT induces neuroplasticity in specific brain regions. Effects in right anterior hippocampus could represent the functional consequences of ECT-induced increases in hippocampal volume reported previously, and could reflect variable seizure foci across patients. Finally, global CBF levels across the entire brain early in treatment may be able to predict which patients will respond successfully to ECT.

**Supported By:** R01MH092301

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**445. Neural Predictors and Correlates of Electroconvulsive Therapy in Late-Life Depression**

Filip Bouckaert1, Annemiek Dols2, Louise Emsell3, François-Laurent Dewinter4, Kristof Vansteelandt5, Stefan Sunaert3, Max Stek2, Pascal Sienaert3, and Mathieu Vandenbulcke5

1University Psychiatric Center KU Leuven, Belgium, 2Department of Psychiatry and the EMGO+ Institute for Health and Care Research, VU University Medical Center Amsterdam, the Netherlands, 3Translational MRI, Department of Imaging and Pathology, KU Leuven, Radiology, University Hospitals Leuven, and University Psychiatric Center KU Leuven, Belgium, 4KU Leuven, University Psychiatric Center KU Leuven, Old-age Psychiatry, Belgium, 5KU Leuven, University Psychiatric Center KU Leuven, Department of Statistics, Belgium, 6KU Leuven, University Psychiatric Center KU Leuven, Academic Center for ECT and Neuromodulation, Belgium

**Background:** Converging evidence suggests that electroconvulsive therapy (ECT) induces neuroplasticity in specific cortico-limbic networks in patients with recurrent depression. Here, we measured cerebral blood flow (CBF) with arterial spin-labeled (ASL) magnetic resonance imaging (MRI) to assess neurofunctional predictors and correlates clinical response to ECT.

**Methods:** Patients ($n=42$) were assessed before ECT, after 2 treatments, and after index (2-4 weeks later). Age- and sex-matched controls were scanned twice ($n=33$), 2-4 weeks apart. Linear mixed-effects models assessed changes in global and voxelwise CBF in responders and non-responders, controlling for age, global CBF, gray-matter content, treatment parameters, and multiple comparisons as appropriate.

**Results:** After ECT index, CBF increased in the right anterior hippocampus. The position and extent of this effect differed between responders and nonresponders, such that responders exhibited a more focal and slightly more posterior regional increase in hippocampal CBF than nonresponders. Positive antidepressant response was also associated with increased CBF in the left dorsal thalamus, and decreased CBF in right temporoparietal cortex. Lower global CBF prior to ECT, and increased CBF after two treatments, both predicted positive antidepressant response.

**Conclusions:** Our data support a growing literature indicating that ECT induces neuroplasticity in specific brain regions. Effects in right anterior hippocampus could represent the functional consequences of ECT-induced increases in hippocampal volume reported previously, and could reflect variable seizure foci across patients. Finally, global CBF levels across the entire brain early in treatment may be able to predict which patients will respond successfully to ECT.

**Supported By:** R01MH092301

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Background: It remains unclear whether neuroimaging can predict ECT response and whether structural changes associated with ECT explain its therapeutic efficacy. We aimed to identify neural predictors of ECT and the extent to which ECT-induced neural changes and clinical or neurotrophic factors.

Methods: Clinical outcome measures 1 week prior to ECT (T0), after the sixth ECT (T1), one week (T2), four weeks (T3) after the last ECT and 6 months after the last ECT (T4). Neuroimaging techniques at T0 and T2 (visual rating scales, manual segmentation of hippocampal volume (HV), voxel based morphometry (VBM), and at T0 only (white matter hyper intensities (WMH), 18F-flutemetamol PET imaging and advanced surface and shape-based methodology) combined with serum Brain Derived Neurotrophic Factor (sBDNF) at T0, T1, T2 and T3.

Results: 1. Structural MRI characteristics (visual rating), vascular burden or late-onset were not associated with response. HV, WMH and amyloid burden did not predict clinical outcome. 2. We observed right-hemispheric GMV increase in caudate nucleus, medial temporal lobe, insula and posterior superior temporal cortex. A correlation was found between increased GMV in caudate nucleus region and psychomotor change but no co-occurrence between changes in mood, HV and sBDNF. We identified subcortical morphological changes with a weak relationship between striatum displacement and psychomotor function.

Conclusions: HV, WMH and amyloid load are not related to ECT response, suggesting ECT should be considered on clinical grounds regardless of markers of age-related brain pathology. Following ECT, structural changes are unrelated to changes in depressive symptomatology, suggesting a complex mechanism of ECT in LLD.

Supported By: Research Foundation - Flanders (FWO) (Dr. Vandenbergulcke).

Keywords: Late Life Depression, Electroconvulsive therapy, Longitudinal Brain Imaging, Neural correlates

446. Predicting ECT Response with Baseline Neuroimaging Data

Christopher Abbott¹ and Jing Sui²

¹University of New Mexico, ²Mind Research Network

Background: Biological markers may be informative in identifying depressed patients who respond to a specific antidepressant treatment. Due to its rapid and robust clinical effects, electroconvulsive therapy (ECT) represents an optimal model to develop and test treatment biomarkers of eventual response.

Methods: Advanced pattern matching and data mining techniques identified structural magnetic resonance imaging (sMRI) networks predictive of recovery from depression from three independent data sets (UNM, n = 38; LIJ, n = 7; and UCLA, n = 10).

Results: For the UNM data set, six grey matter (GM) regions were repeatedly identified as predictive of future response (change in depression ratings) at r=0.90 and classified eventual remitters with high precision (sensitivity 88.9%, specificity 90.9%). We further tested these potential biomarkers using pre-ECT GM data from two independent, demographically-matched data sets from UCLA and LIJ; high estimation accuracy of eventual change in depression severity and predictive accuracy of remitter were also achieved (UCLA: r = 0.71, sensitivity 100%, specificity 87.5%; LIJ: r = 0.77, sensitivity 66.7%, specificity 100%). Two of the six extracted predictive regions (right supplementary motor/ superior frontal and right post-central gyrus) showed GM volume changes over the four-week assessment interval; the remaining predictive regions (left hippocampal/parahippocampal, left inferior temporal, left middle frontal and right angular gyrus) did not vary significantly with treatment.

Conclusions: These results suggest a particular network of GM features can serve as a prognostic sMRI biomarker to guide personalized treatment decisions. Findings also suggest that antidepressant response involves interactions between treatment predictive and treatment responsive networks.

Supported By: NIMH 1R01 MH111826-01 and 2P20GM103472-01 (Abbott and Sui)

Keywords: Depression, Structural MRI, Electroconvulsive therapy, Prediction of Treatment Outcome, Machine learning

447. Establishing a Multi-Site Investigation of the Neural Mechanisms Underlying Response to Electroconvulsive Therapy

Leif Oltedal¹, Hauke Bartsch², Ole Johan Evjenth Sarhaug³, Ute Kessler³, Anders M Dale², Ketil J Oedegaard³, and for GEMRIC⁵

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Background: It is unclear how structural and functional brain changes after ECT associate with stimulus parameters and clinical outcome. Larger studies accounting for individual differences in clinical and treatment parameters are necessary to target biological factors relating to or predictive of antidepressant response.

Methods: A systematic literature search identified contributing groups and the Global ECT-MRI Research Collaboration (GEMRIC) was formed. Methods for standardization of multi-site clinical data were established and a common data portal for mega-analysis developed. The image processing pipeline includes pre-processing with corrections for scanner specific distortions, FreeSurfer and unbiased estimates of regional anatomical change with Quarc.

Results: The GEMRIC data sample consists of 345 subjects (age range 19-86; ~ 60 % female, ~ 85% unipolar depression) from 14 sites with 2 - 4 imaging time points. The processing pipeline was evaluated on data from one site with two scanners. The effect sizes (Cohen’s d) of Quarc regional ECT-induced anatomical volume change were typically in the range 0.5 – 2. The pattern of change was broadly distributed and lateralized to the side of the stimulus; e.g. the volume of the right and left temporal pole regions changed by 4.9 (p<0.0001) and 2.6 % (p<0.05), respectively (n=19), compared to healthy controls (n=9).

Conclusions: Standardized image processing and statistical tools for analysis combined with the large and heterogeneous dataset will provide new opportunities to investigate factors mediating and predictive of clinical outcomes, which may
ultimately lead to more effective personalized treatment approaches.

**Supported By:** Western Norway Regional Health Authority, Haukeland University Hospital and the University of Bergen, Norway.

**Keywords:** ECT, Structural MRI, Longitudinal Brain Imaging, Major Depression

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**SYMPOSIUM**

**Bipolar Disorder with Comorbid Binge Eating Disorder – Validation of a Clinically Important Sub-Phenotype**

Friday, May 19, 2017 - 3:00 PM - 5:00 PM

Chair: Marin Veldic

Co-Chair: Susan McElroy

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448. Evidence for a Role of Binge Eating and Obesity in Bipolar Disorder Genetic Risk: Genome-wide Associations in PRR5-ARHGAP8 and TCF7L2

Alfredo Cuellar Barboza1, Susan McElroy2, Stacey Winham3, Colin Colby3, Euijung Ryu4, Miguel Prieto5, Mark Frye6, and Joanna Biernacka3

1UANL, 2Lindner Center of HOPE/University of Cincinnati College of Medicine, 3Mayo Clinic, 4Universidad de los Andes

**Background:** Bipolar disorder’s (BD) genetic architecture may be modified by interrelated heritable traits. For example adiposity-related traits, binge eating behavior (BE) and obesity, are positively associated with BD and compose complex subphenotypes of distinctive morbidity. We sought to perform genome wide analyses (GWA) of BD accounting for BE, body mass index (BMI) and BMI-gene interactions.

**Methods:** We conducted a BE GWA using 968 BD cases and 777 controls. We used logistic regression analyses comparing BD cases with and without BE, adjusted for 4 principal components. Top variants were assessed for replication in an independent population (N=1001). To investigate obesity, we used 388 BD cases and 1020 healthy controls with available BMI data. We performed GWAs of the genetic effects accounting for BMI, and SNP–BMI interactions. Results from the top finding of this GWA were replicated using an independent sample of 662 BD cases and 616 controls.

**Results:** For BE no variants reached genome-wide significance in the separate analyses. However, a meta-analysis provided genome-wide significant evidence of association with rs726170 (OR=1.91, P=3.05E-08) in a read-through gene PRR5-ARHGAP8 in BD case-only analysis. We found a genome-wide significant hit in rs12772424 (P=2.85E–8) an intronic variant in TCF7L2, with interaction effects that indicate that higher BMI confers higher BD risk in low allele carriers. This finding was independently replicated in the Mayo sample (P=0.011).

**Conclusions:** BE and obesity in BD are associated with common variants in read-through genes potentially related to feeding behavior and TCF7L2, the effector of the canonical Wnt signaling pathway, respectively.

449. Preclinical Models for the Study of Binge Eating Disorder

Michael Statnick

Eli Lilly and Company

**Background:** Binge eating disorder (BED) affects roughly 1–4% of the U.S. population. BED is characterized by repeated episodes of eating unusually large amounts of food in a short period of time without engaging in compensatory behaviors. Preclinical animal models of BED have been developed employing caloric restriction and/or exogenous stressors to stimulate binge-like eating. We have developed a preclinical model of BED in mice that does not require caloric restriction or stress.

**Methods:** Mice were randomized according to body weight, and divided into one of three experimental groups; chow, continuous access, or intermittent access. Chow controls received unlimited access to a standard rodent chow diet. Continuous access animals had ad libitum access to both standard chow and a high energy diet (HED). The intermittent access group received standard chow ad libitum and HED for 24-h once weekly. For drug treatments, animals were randomized based on 2.5-hr HED intake and administered either vehicle, or drug (fluoxetine, baclofen, topiramide, or various opioid antagonists) in a dose volume of 1 mg/ml.

**Results:** Mice under the protocol exhibited a significantly elevated intake of HED on access days. The increased intake of HED was consistent across multiple bingeing cycles. Interestingly, opioid antagonists, fluoxetine and baclofen were all effective in reducing binge-like eating, while topiramate was not active.

**Conclusions:** Preclinical models exhibit many of the hallmark characteristics of BED. As known clinically efficacious compounds reduce binge-like eating in these rodent models, these may be useful in identifying novel pharmacological treatments for BED.

**Supported By:** Eli Lilly and Company

**Keywords:** Binge Eating Disorder, Rodents, Fluoxetine, Opioid system

450. In Bipolar Disorder, SLC1A2 Promoter Hypomethylation is Associated with Binge Eating Disorder and Nicotine Dependence

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1Mayo Clinic, 2Department of Molecular Pharmacology & Experimental Therapeutics, Mayo Clinic, Rochester MN, 32Neurobiology of Disease Program, Mayo Graduate School, Mayo Clinic, Rochester, MN, 4Department of Psychiatry & Psychology, Mayo Clinic Depression Center; Division of Biomedical Statistics and Informatics, Mayo

**Supported By:** Marriott Family Foundation and Mayo Clinic’s Center for Individualized Medicine.

**Keywords:** BMI, Binge Eating Disorder, Bipolar Disorder, GWAS

**Friday Abstracts**
Clinic, Rochester, MN; 6Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN; 7Lindner Center of HOPE/University of Cincinnati College of Medicine, 8Mayo Clinic College of Medicine

Background: Bipolar disorder (BP) is influenced by environmental factors, which may, via epigenetic modulation differentially affect illness presentation. Glutamatergic dysregulation has been reported in BP but also in binge eating disorder (BE) and substance use disorders. The contribution of excitatory amino acid transporter 2 (EAAT2), encoded by SLC1A2, epigenetics to BP is unknown and was the focus of this investigation.

Methods: High resolution melting PCR (HRM-PCR) and thymine-adenine cloning were conducted to examine promoter methylation of the SLC1A2 in blood DNA from BP patients (n=150) with or without addiction to food (defined as BE), alcohol (AA), nicotine (ND), and controls (n=32). HRM-PCR primers targeted two areas within the proximal promoter region of the SLC1A2 (amplicons 1&2).

Results: HRM-PCR: One-way ANOVA demonstrated differences in methylation across the six groups for both amplicons (p<0.0003, p<0.0001). In amplicon 1, post-hoc pairwise tests adjusted for multiple comparisons demonstrated hypomethylation in BP with ND (p=0.003) and BE (p=0.002). In amplicon 2, BP was associated with hypomethylation (p<0.0001) while BP with addictions [AA (p=0.002), ND (p<0.0001), ND+AA (p=0.0001), and BE (p<0.0001)] were associated with hypomethylation. Direct sequencing identified increased methylation in in BP, but decreased methylation in BP with addiction.

Conclusions: To our knowledge, the current study presents the first evidence suggesting that methylation within the SLC1A2 promoter may be modified by BP and addiction. Future carefully designed longitudinal study on a larger sample with serial evaluations of epigenetic changes is warranted in order to add more clarity to understanding of the complicated interactions between BE, addiction, and BP.

Supported By: Mayo Foundation for Medical Education and Research as well as the J. Willard and Alice S. Marriott Foundation grant to Dr. Veldic.

Keywords: EAAT2, DNA methylation, Glutamate, Bipolar Disorder, Binge Eating Disorder

451. Treatment of Binge Eating Disorder
Susan McElroy

Lindner Center of HOPE/University of Cincinnati College of Medicine

Background: In the final talk we will provide an overview of empirically-based treatments of binge eating disorder (BED), including cognitive behavior therapy (CBT), interpersonal therapy (IPT), lisdexamfetamine dimesylate (LDX), anticonvulsants, and weight-loss agents. Substantial effectiveness has been shown for (CBT) and interpersonal therapy (IPT), which are both more effective than behavior weight loss therapy (BWLT) for reducing binge eating over the long term, but are not associated with clinically significant weight loss. The stimulant pro-drug lisdexamfetamine (LDX) is the only drug approved by the FDA for the treatment of BED specifically, it is approved for moderate to severe BED in adults. Though associated with weight loss, LDX is not approved for the treatment of obesity. The clinical trials supporting this indication will be reviewed. The anticonvulsants topiramate and zonisamide also decreases binge eating behavior and excessive body weight in BED, but their use is limited by the drugs’ adverse event profile. A small study of lamotrigine showed the drug was not superior to placebo for reducing binge eating, but was associated with improved metabolic variables. Antidepressants may be modestly effective over the short term for reducing binge eating behavior and comorbid depressive symptoms, but are not associated with clinically significant weight loss. Agents currently undergoing study for BED will also be discussed, including the norepinephrine dopamine reuptake inhibitor dasotraline, the GLP-1 analogue liraglutide, and opiate antagonists. Though most studies of BED have excluded persons with bipolar disorder, the treatment of patients with both conditions will be discussed.

Methods: NA

Results: NA

Conclusions: NA

Keywords: Bipolar, binge eating, lisdexamfetamine, anticonvulsants, weight-loss drugs

POSTER SESSION
Friday, May 19, 2017 - 5:00 PM - 7:00 PM
Sapphire CP

452. Longitudinal Study of Cognitive and Emotional Brain Correlates of PTSD in Females Rape Victims
Helen Clery1, Frédéric Andersson2, and Wissam El-Hage1

1University Hospital of Tours, 2INSERM U930 Imaging and Brain

Background: Several neuropsychological studies have shown in patients with post-traumatic stress disorder (PTSD) deficits in impulse control and preferential allocation of attentional resources to potentially threatening stimuli. Whereas these behavioural symptoms are linked to re-experiencing and are thus in the core of the symptomatology of PTSD, their neurobiology has been rarely investigated.

The goal of this longitudinal study is to characterize early modifications of brain activity in response to cognitive and emotional load in females rape victims compared to healthy control one month after the trauma and six months later.

Methods: For this longitudinal study, each volunteer (25 rape victims and 20 controls) participated in two fMRI sessions; T1 at 4 ± 2 weeks and T2 at 24 ± 2 weeks after the traumatic event. Three cognitive and emotional tasks are used. Coupled with the neuroimaging acquisitions, biological measurements reflecting the level of stress of participants are recorded and neuropsychological assessments of attention and memory abilities are done.

Results: Results do not show any significant difference between rape victims and controls for both neuropsychological evaluations and salivary cortisol measurements, neither at T1 nor at T2. fMRI

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results show that at both T1 and T2, rape victims display hyperactivation of frontal, anterior cingulate and parietal regions compared to controls, only in response to emotional stimulations. **Conclusions:** This pathophysiological study improves our knowledge on the development of PTSD, especially on the early changes in the architecture of brain regions involved in attention abilities and in emotion regulation of victims of severe psychological trauma.

Supported By: University Hospital of Tours

Keywords: PTSD - Posttraumatic Stress Disorder, Longitudinal Brain Imaging, Emotional processing

453. Exploration of Functional Networks Supporting Emotion Inhibition in Anxiety

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¹University of California, Los Angeles, ²University of Illinois at Urbana-Champaign, ³University of Delaware

**Background:** Generalized anxiety disorder (GAD) is associated with decreases in performance on emotion-word Stroop (EWS) tasks relative to healthy individuals (Williams et al., 1996). Neural mechanisms associated with this reduced inhibition of a reaction to emotional stimuli are poorly understood. The present study utilized graph-theoretic analysis of fMRI data during an emotion inhibition task, the EWS, to identify key changes in the structure and function of brain networks associated with emotion inhibition in healthy individuals and in individuals with elevated GAD symptom severity (GAD).

**Methods:** Graph theory was used to analyze fMRI data collected during an EWS task from 103 individuals recruited from the community. Each participant completed a clinical interview (SCID) during which GAD was rated.

**Results:** Two networks were associated with emotion inhibition during the EWS task: one involving hyperconnectivity to prefrontal cortex and one involving hyperconnectivity to thalamus. Anxiety symptoms predicted hyperconnectivity in a third network involving caudate nucleus and less resilient global network organization during inhibition of response to emotionally-valenced words.

**Conclusions:** These findings indicate that GAD is associated with a network structure during inhibition of emotional stimuli that is more vulnerable to damage or dysregulation. In non-anxious individuals, a clear interplay between two networks (top-down attention control and bottom-up emotion salience) can be seen. The network associated with emotion inhibition in GAD (centering on caudate nucleus) indicates an inefficient restructuring of functional networks and a possible mechanism by which emotion inhibition deficits occur in GAD.

Keywords: Anxiety, Emotion, Inhibition, BOLD fMRI, graph theory

454. Neural Indices of Cognitive Emotion Regulation and Course of PTSD Symptom Severity in OEF/OIF/OND Veterans

Jacklynn Fitzgerald¹, Julia DiGangi¹, Autumn Kujawa², Darrin Aase³, Justin Greenstein⁴, Eric Proescher⁵

¹University of Illinois at Chicago, ²Penn State College of Medicine, ³Jesse Brown VA Medical Center

**Background:** Many combat-exposed veterans develop posttraumatic stress disorder (PTSD) following deployment, although there is substantial variability in the natural course of illness. Emotion dysregulation is a core feature of PTSD, and cross-sectional work reveals that abnormal neural response during volitional regulation—measured using the late positive potential (LPP)—correlates with symptom severity. Whether abnormal response during regulation of emotion predicts PTSD symptoms over time is unknown. The current study examined the LPP during emotional responding and regulation as predictors of PTSD symptoms over one year.

**Methods:** OEF/OIF/OND combat-exposed veterans completed an Emotion Regulation Task (ERT) during electroencephalogram recording, along with the Clinician Administered PTSD Scale (CAPS) at that time (N=91), 6 months (N=52) and 1 year (N=42) later. During ERT, participants viewed negative pictures (7s); partway through they were asked to “reappraise” (i.e., reduce negative affect) or “look” (i.e., passively experience). The LPP was examined as a measure of emotional arousal; during Reappraisal, change in LPP (ΔLPP) was calculated using a Look-Reappraisal difference wave. Multilevel mixed modeling was used to predict CAPS over time using LPP and ΔLPP.

**Results:** Symptom severity declined over time (b=-4.21, t(122.69)=-3.56, p=0.001) and greater combat exposure predicted higher CAPS (b=0.44, t(74.43)=3.07, p=0.003). Controlling for these effects and anxiety/depression severity, smaller ΔLPP during reappraisal—indicative of ineffective emotion regulation—predicted greater symptoms across time (b=-0.64, t(84.54)=-2.64, p=0.010).

**Conclusions:** These findings reveal that deficiency in down-regulating emotional arousal—measured neurally by change in the LPP—may be a useful predictor of PTSD symptoms in combat-exposed veterans.

Supported By: Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and the Veterans Affairs Merit Review Program Award (I01 BX0007080)

Keywords: PTSD Symptom Severity, Late Positive Potential, Event Related Potentials, Emotion Regulation, Cognitive Reappraisal

455. Examining the Relationship between the Late Positive Potential during Emotion Regulation and Self-Reported Emotion Regulation Tendencies in Anxiety Disorders

Kerry Kinney, Katie Burkhorse, Amy E Kennedy, and Heide Klumpp

University of Illinois at Chicago

**Background:** Anxiety disorders are associated with emotion dysregulation as indicated by less use of adaptive regulation
Methods: Electroencephalography was recorded during an emotion regulation task (ERT) in 54 patients (42 social phobia, 9 generalized anxiety disorder, 3 panic disorder) and 28 healthy controls. In the ERT, participants used a cognitive approach (i.e., reappraisal) to reduce emotional reactivity to aversive images, which was contrasted with looking at aversive images. LPP was evaluated along early, middle, and late time windows. The Emotion Regulation Questionnaire (ERQ) assessed self-reported reappraisal/suppression. Two 2 (group) x 2 (condition) x 3 (time windows) ANCOVAs were conducted, with self-reported reappraisal (ERQ-R) and suppression (ERQ-S) entered as covariates of interest, respectively.

Results: Healthy controls reported more frequent reappraisal use than patients (p < .001); no group effects emerged for suppression (p = .08). The ERQ-R ANCOVA yielded null results. ERQ-S analysis revealed a time, condition, and regulation interaction (p = .01). Follow-up analyses revealed a positive correlation between ERQ-S and late LPP when viewing negative images.

Conclusions: Greater tendency to use suppression was associated with greater sustained LPP when attending to negative images across participants. Thus, individual differences in suppression are predictive of sustained emotional reactivity to negative stimuli.

Supported By: R01-MH086517; T32-MH067631

Keywords: pediatric anxiety, Prediction of Treatment Outcome, Neuroimaging, Attention, emotional face processing

457. Fear Extinction Mechanisms and the Link to Exposure Therapy Outcome in Specific Phobia: A Pilot Study

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Maastricht University

Background: Fear extinction is the decrement in conditioned fear responses occurring with repeated presentation of a conditioned threat stimulus without reinforcement. Exposure-based treatments (ET) are thought to rely on extinction learning mechanisms. The current study provides novel unpublished data exploring whether the neurobehavioral mechanisms of fear extinction learning and extinction recall can predict exposure therapy success in specific phobia.

Methods: Individuals aged 16-25 with a spider phobia (SP; n = 18) were included. All individuals underwent a 3-day fMRI fear conditioning, extinction and extinction recall paradigm with geometrical shapes as conditioned threat (CS+) and safety (CS-) stimuli. Generalization stimuli (GS) were additionally shown during extinction recall. Fear, valence, shock expectancy and blood-oxygen-level-dependent (BOLD) response were measured. Next, participants underwent one session of exposure therapy (n = 18). Before and after therapy, phobic symptoms were measured with the Fear of spiders questionnaire (FSQ) and a behavioral approach test (BAT).

Results: Regression analyses showed a trend for better extinction retention predicting a higher increase in BAT from pre-to-post therapy (p = .08). Furthermore, a higher increase in BAT from pre-to-post therapy tended to be associated with higher valence ratings for GS during extinction recall (p = .08). A lower phobia score on the FSQ from pre-to-post therapy was marginally associated with a lower valence for the CS+ during extinction recall (p = .07). Neuroimaging results were found in the fear extinction network, compromising the vmPFC, hippocampus, and amygdala.

Conclusions: Our results point out that exposure therapy outcome can be predicted by enhanced threat-safety identification at extinction recall.

456. Neural Correlates of Implicit Emotion Processing in Pediatric Anxiety: Changes with and Predictors of Treatment Response

Katie Burkhouse1, Autumn Kujawa2, Heide Klumpp3, Kate Fitzgerald4, Christopher Monk4, and K. Luan Phan3

1University of Illinois at Chicago Department of Psychiatry, 2Penn State College of Medicine, 3University of Illinois at Chicago, 4University of Michigan

Background: The current study examined the neural correlates of directing attention toward (explicit emotion processing) and away (implicit emotion processing) from emotional faces in relation to pediatric anxiety treatment response. Based on findings that patients with anxiety disorders exhibit less anterior cingulate cortex (ACC) recruitment in the presence of emotional face distractors, we expected that recruitment of the ACC during implicit emotion processing would influence treatment response. Secondary analyses were conducted to determine whether ACC activation during implicit emotion processing changed pre-to-post treatment.

Methods: 62 youth (age 7-18 years) with and without anxiety disorders completed a task matching emotional faces (explicit emotion processing) or matching shapes in the context of emotional face distractors (implicit emotion processing) during fMRI. Anxious youth were enrolled in 10 weeks of treatment, consisting of either SSRI medication or cognitive behavior therapy (CBT). Following 10 weeks, the youth repeated the emotional-attention task. Treatment response was assessed via the Pediatric Anxiety Rating Scale.

Results: Reduced activation in the dorsal ACC during implicit fear processing predicted a greater reduction in anxiety severity pre-to-post treatment, t-value = 3.47, p = .03. Recruitment of the rostral ACC in response to implicit threat processing also increased following both CBT and SSRIs among anxious youth, F-value = 4.19, p = .04, but not among healthy youth.

Conclusions: The current findings are the first to demonstrate that reduced recruitment of the ACC during attentional control appears to resolve following treatment and is predictive of treatment response, possibly reflecting an improvement in attentional control processes following treatment with CBT and SSRIs.

Supported By: R01-MH086517; T32-MH067631

Keywords: pediatric anxiety, Prediction of Treatment Outcome, Neuroimaging, Attention, emotional face processing

(i.e., ‘reappraisal’) and more frequent use of maladaptive regulation (i.e., ‘suppression’) in daily life. The late positive potential (LPP) reflects emotional reactivity, which is expected to decrease during successful ER. It is unclear whether LPP in ER tracks self-reported ER tendencies in anxiety disorder. This study attempts to address this gap.

Methods: Electroencephalography was recorded during an emotion regulation task (ERT) in 54 patients (42 social phobia, 9 generalized anxiety disorder, 3 panic disorder) and 28 healthy controls. In the ERT, participants used a cognitive approach (i.e., reappraisal) to reduce emotional reactivity to aversive images, which was contrasted with looking at aversive images. LPP was evaluated along early, middle, and late time windows. The Emotion Regulation Questionnaire (ERQ) assessed self-reported reappraisal/suppression. Two 2 (group) x 2 (condition) x 3 (time windows) ANCOVAs were conducted, with self-reported reappraisal (ERQ-R) and suppression (ERQ-S) entered as covariates of interest, respectively.

Results: Healthy controls reported more frequent reappraisal use than patients (p < .001); no group effects emerged for suppression (p = .08). The ERQ-R ANCOVA yielded null results. ERQ-S analysis revealed a time, condition, and regulation interaction (p = .01). Follow-up analyses revealed a positive correlation between ERQ-S and late LPP when viewing negative images.

Conclusions: Greater tendency to use suppression was associated with greater sustained LPP when attending to negative images across participants. Thus, individual differences in suppression are predictive of sustained emotional reactivity to negative stimuli.

Supported By: MH093679

Keywords: Anxiety Disorders, late positive potential, Emotion Regulation, Emotional Suppression, Cognitive Reappraisal
**458. The Role of Trait Gratitude on Functional Brain Activation Changes when Anticipating Negative Events in Individuals with PTSD**

Anna Alkozei, Ryan Smith, Andrew Fridman, Alyssa Dormer, Skye Challener, and William D.S. Killgore

University of Arizona

**Background:** While higher levels of trait gratitude have been associated with reduced posttraumatic stress disorder (PTSD) symptom severity and improved emotion regulation abilities, the neurobiological basis of this association is unknown. We aimed to investigate how differences in trait gratitude were associated with functional brain activation changes in individuals with PTSD when anticipating negative stimuli.

**Methods:** Fifteen individuals (53% female) with a clinical diagnosis of PTSD completed an emotional anticipation task during fMRI. Participants also completed the Gratitude Questionnaire (GQ6). Whole brain analyses were conducted for the negative anticipation > uncertain anticipation contrast using a height intensity threshold of p < .001 while protecting against Type I error through a cluster-corrected extent threshold of 62 (FDR correction of p < .05).

**Results:** There was a significant negative association between GQ6 scores and activation within the right insula (x = 34, y = 16, z = 10; p = .03), bilateral rACC (x = -4, y = 36, z = 4; p < .001), and the left precuneus (x = -12, y = -66, z = 32; p = .02). There was also a significant positive association between rACC-insula functional connectivity and GQ6 scores during negative anticipation (T = 2.66, p = .04).

**Conclusions:** In a sample of patients with PTSD, those with higher gratitude show evidence of reduced hyperactivation within the insula and greater connectivity of the rACC with the insula when anticipating negative stimuli, a finding that may be beneficial for individuals with PTSD.

**Supported By:** Stichting De Weijerhorst

**Keywords:** Exposure Therapy, fMRI, Phobia, Extinction Learning and Recall

**460. Altered Neural Habituation to Emotional Faces in Pediatric and Adult Bipolar Disorder**

Maria Kryza-Lacombe¹, Jillian Lee Wiggins², Melissa A. Brotman³, Jill Weisberg⁴, Carly Farrington⁴, Raechel Rodda², Kenneth Towbin³, Daniel S. Pine³, and Ellen Leibenluft³

¹SDSU/UCSD Joint Doctoral Program in Clinical Psychology, ²SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego State University, ³Emotion Development Branch, National Institute of Mental Health, National Institutes of Health, ⁴Department of Psychology, San Diego State University

**Background:** Many leading theories suggest that the neural processes underlying the experience of one’s own emotional reactions partially overlap with those underlying bodily perception (i.e., proprioception, somatosensation, and interoception). However, the goal-directed maintenance of one’s own emotions in working memory (EWM) has not yet been compared to WM maintenance of one’s own bodily reactions (BWM). The role of trait differences in emotional awareness (EA) has also not been examined in this context.

**Methods:** In this study we contrasted WM maintenance of emotional vs. bodily reactions to affective stimuli in 26 healthy individuals while they underwent functional magnetic resonance imaging. Participants also completed the Levels of Emotional Awareness Scale (LEAS) as a measure of EA. We examined the a priori hypothesis that individual with greater EA would also show greater differences in medial prefrontal cortex (MPFC) activation between EWM and BWM.

**Results:** We observed that MPFC activation during EWM (relative to BWM) was positively associated with EA (r = .38, p = .027, 1-tailed). Whole-brain analyses otherwise showed no activations that were greater in EWM than BWM. The contrast of BWM > EWM highlighted activations in several clusters spanning the left and right parietal/somatosensory cortex, precuneus and posterior cingulate, DLPFC, posterior DMpFC and supplementary motor area (SMA), and other regions (p < .05, FDR-corrected).

**Conclusions:** In conjunction with previous literature, our findings support a central role of maintaining body state representation during EWM. They also suggest greater engagement of MPFC-mediated conceptualization processes during EWM in those with higher EA.

**Keywords:** Emotion-cognition interaction, Interception, Working memory, medial prefrontal cortex


Ryan Smith, Richard Lane, Anna Alkozei, Jennifer Bao, Courtney Smith, Anna Sanova, Matthew Nettles, and William Killgore

University of Arizona, Department of Psychiatry

**Background:** Failure to habituate to repeated presentation of emotional faces has been shown to contribute to socioemotional symptoms. Previous research indicates that children and adults with bipolar disorder (BD) show behavioral deficits in face emotion processing including abnormal prefrontal cortex and amygdala activation. However, no study had yet examined neural habituation to emotional faces in BD. Moreover, despite evidence that BD differs across the lifespan, little work has compared neural profiles of pediatric vs. adult BD.

**Supported By:** USAMRAA

**Keywords:** PTSD, Gratitude, Emotional Anticipation, BOLD fMRI

**Friday Abstracts**

**Supported By:** Stichting De Weijerhorst

**Keywords:** Exposure Therapy, fMRI, Phobia, Extinction Learning and Recall

**458. The Role of Trait Gratitude on Functional Brain Activation Changes when Anticipating Negative Events in Individuals with PTSD**

Anna Alkozei, Ryan Smith, Andrew Fridman, Alyssa Dormer, Skye Challener, and William D.S. Killgore

University of Arizona

**Background:** While higher levels of trait gratitude have been associated with reduced posttraumatic stress disorder (PTSD) symptom severity and improved emotion regulation abilities, the neurobiological basis of this association is unknown. We aimed to investigate how differences in trait gratitude were associated with functional brain activation changes in individuals with PTSD when anticipating negative stimuli.

**Methods:** Fifteen individuals (53% female) with a clinical diagnosis of PTSD completed an emotional anticipation task during fMRI. Participants also completed the Gratitude Questionnaire (GQ6). Whole brain analyses were conducted for the negative anticipation > uncertain anticipation contrast using a height intensity threshold of p < .001 while protecting against Type I error through a cluster-corrected extent threshold of 62 (FDR correction of p < .05).

**Results:** There was a significant negative association between GQ6 scores and activation within the right insula (x = 34, y = 16, z = 10; p = .03), bilateral rACC (x = -4, y = 36, z = 4; p < .001), and the left precuneus (x = -12, y = -66, z = 32; p = .02). There was also a significant positive association between rACC-insula functional connectivity and GQ6 scores during negative anticipation (T = 2.66, p = .04).

**Conclusions:** In a sample of patients with PTSD, those with higher gratitude show evidence of reduced hyperactivation within the insula and greater connectivity of the rACC with the insula when anticipating negative stimuli, a finding that may be beneficial for individuals with PTSD.

**Supported By:** Stichting De Weijerhorst

**Keywords:** Exposure Therapy, fMRI, Phobia, Extinction Learning and Recall


Ryan Smith, Richard Lane, Anna Alkozei, Jennifer Bao, Courtney Smith, Anna Sanova, Matthew Nettles, and William Killgore

University of Arizona, Department of Psychiatry

**Background:** Failure to habituate to repeated presentation of emotional faces has been shown to contribute to socioemotional symptoms. Previous research indicates that children and adults with bipolar disorder (BD) show behavioral deficits in face emotion processing including abnormal prefrontal cortex and amygdala activation. However, no study had yet examined neural habituation to emotional faces in BD. Moreover, despite evidence that BD differs across the lifespan, little work has compared neural profiles of pediatric vs. adult BD.

**Supported By:** USAMRAA

**Keywords:** PTSD, Gratitude, Emotional Anticipation, BOLD fMRI

**Friday Abstracts**
Methods: Adolescents (n=24; mean age=16.5 years, SD=2.4) and adults (n=33; mean age=38.2 years, SD=11.1) with BD as well as healthy adolescents (n=29; mean age=15.1 years, SD=2.4) and adults (n=22; mean age=29.4 years, SD=7.2) performed a face emotion-labeling task during functional magnetic resonance imaging acquisition.

Results: Whole-brain analyses revealed Diagnosis x Age interactions predicting habituation of medial prefrontal cortex (xyz = 6,41,43; k=61; F(1,101)=13.67, p<.05 corrected) and lingual gyrus (xyz = 1,-79,-6; k=42; F(1,101)=16.11, p<.05 corrected) to emotional faces. Post-hoc comparisons revealed that whereas healthy youths decrease in activation with repeated presentation of faces (i.e., habituate), youths with BP increase in activation (i.e., sensitization). Adults (healthy and with BP) did not significantly change in activation over the task. There was also a trend for Diagnosis x Age in the amygdala region of interest (p=.08).

Conclusions: These findings demonstrate that altered habituation to faces may be involved in pediatric BD. The results furthermore suggest that adult and pediatric BD may involve different neural mechanisms. These results have implications for facilitating developmentally sensitive diagnosis and treatment for BD

Supported By: NIMH Intramural Research Program

Keywords: fMRI, Bipolar Disorder, Faces, brain, development

461. Perceived Social Standing Predicts Hippocampal Volume over and above the Effects of Income

Monica Ellwood-Lowe, Kathryn Humphreys, Matthew Sacchet, M Catalina Camacho, Sarah Ordaz, and Ian Gotlib
Stanford University

Background: Low socioeconomic status (SES) is a risk factor for negative cognitive, social, and emotional outcomes. Researchers investigating the neurobiological consequences of SES have found that low SES is associated with reduced hippocampal volume. These studies have assessed objective SES; however, subjective social status (SSS) may be a stronger predictor of adverse outcomes. In this study we examined the relative power of objective and subjective status to predict hippocampal volume in early adolescents.

Methods: 122 adolescents (age 9.2-14.0, M=11.4; 54% female) matched in pubertal status (tanner stage 1-3.5, M=2.0) completed a high-resolution T1-weighted anatomical MRI scan. Parents reported actual income and children ranked their fathers on a “social ladder,” assessing subjective social standing.

Results: Using hierarchical linear regression, actual income increased the prediction of bilateral hippocampal volume after controlling for age, sex, tanner stage, and intracranial volume (β=.16, t=2.0, p=.05, ΔR²=.03). Further, SSS significantly increased the prediction of hippocampal volume over and above income and the covariates (β=.20, t=2.38, p=.02, ΔR²=.04), with higher SSS predicting larger hippocampal volume. Participant sex significantly moderated the effects of SSS on hippocampal volume (interaction: β=-.59, t=-2.13, p=.04, ΔR²=.03): whereas in girls SSS predicted an additional 10% of hippocampal volume (β=.35, t=2.83, p<.01), in boys SSS was unrelated to hippocampal volume (β=.04, t=.29, p=.78).

Conclusions: This is the first study to show that SSS predicts hippocampal volume above and beyond the effects of income in adolescents. These findings have important implications for understanding how SES affects risk for psychopathology, particularly in girls.

Supported By: NIMH Grant R01-MH101495

Keywords: Socioeconomic factors, early adversity, subjective social status, Hippocampal Volume

462. Looming Threats and Animacy: Reduced Responsiveness in Youth with Disruptive Behavior Disorder

Stuart White1, Laura Thornton1, Kathleen Crum1, Joseph Leshin2, Roberta Clanton3, Stephen Sinclair2, Dionne Coker-Appiah4, Harma Meffert1, Soonjo Hwang5, and R. James Blair6
1Boys Town National Research Hospital, 2Section on Affective Cognitive Neuroscience, NIMH, NIH, 3University of Birmingham, 4Georgetown University School of Medicine, 5University of Nebraska Medical Center, 6Section on Affective Cognitive Neuroscience, NIMH, NIH; Boys Town National Research Hospital

Background: Atypical responses in threat circuitry (amygdala, periaqueductal gray [PAG]) have been implicated in the development of Disruptive Behavior Disorders (DBDs; Conduct Disorder/Oppositional Defiant Disorder). However, relatively little neuro-imaging work has examined the extent to which Callous-Unemotional (CU) Traits modulate this responsiveness or whether disrupted responsiveness is seen for animate and inanimate threats.

Methods: 31 youth with DBDs and 27 typically developing youth, matched for IQ, age and gender, completed a threat paradigm during fMRI. The paradigm involved the presentation of (i) threatening and animate (e.g. snarling dogs); (ii) threatening and inanimate (e.g. pointed gun); (iii) neutral and animate (e.g. sitting rabbit); or neutral and inanimate (e.g. a mug) images which loomed towards or receded from the participant.

Results: Youth with DBDs showed reduced responsiveness to threat information within basic threat circuitry and particularly to animate (relative to inanimate) threat stimuli within inferior frontal gyrus, middle frontal gyrus and inferior parietal cortex. CU traits did not modulate responsiveness to threat information within basic threat circuitry, but were inversely associated with: (i) response to mid-level threat stimuli within frontal cortex, superior temporal gyrus and inferior parietal cortex; and (ii) animate stimuli within posterior cingulate cortex.

Conclusions: Youth with DBDs show generally reduced threat responsiveness that was only modulated by level of CU traits in cortical regions, not basic threat systems. Reduced responses specifically to mid-level threats in youth with DBDs suggest that the threat circuitry is insensitive as opposed to completely dysfunctional, which has potential implications for psychopharmacological intervention.
463. Neural Systems Underlying Youth Irritability: Investigating Disrupted Emotional Responsiveness as a Risk Factor

Kathleen Crum1, Karina Blair2, Joseph Aloii, Harma Meffert3, Stuart White3, Patrick Tyler3, Abraham Killanin3, Kathryn Adams3, Kayla Pope4, and James Blair2

1Boys Town National Research Hospital, 2Center for Neurobehavioral Research, Boys Town National Research Hospital; University of Nebraska Medical Center, 3Center for Neurobehavioral Research, Boys Town National Research Hospital, 4Center for Neurobehavioral Research, Boys Town National Research Hospital; Creighton University

Background: Increased levels of irritability are a feature of a number of developmental disorders, and are associated with considerable impairment and poor long-term prognoses. Indeed, research has linked irritability to affective, anxiety, and behavior disorders, as well as adverse educational, occupational, and mental health outcomes into adulthood. Overall, the literature suggests that irritability represents a potential marker of underlying dysregulation related to psychopathology. However, an understanding of the neural systems that result when compromised, in increased irritability remains in its infancy. It could be suggested that increased irritability might be related to increased threat responsiveness and/or deficient emotional regulation.

Methods: To test this hypothesis, youth in a residential care facility and the surrounding community (N=122) performed the affective Stroop task during fMRI. This task allows both facility and the surrounding community (N=122) performed the affective Stroop task during fMRI. This task allows both

Results: Results indicated that level of irritability, as indexed by the Affective Reactivity Index, was not related to the functional integrity of regions implicated in top down attentional control that can automatically reduce emotional responsiveness.

Conclusions: In conclusion, these data suggest that increased emotional responsiveness, irrespective of top down attentional emotional regulation integrity, is a risk factor for increased levels of irritability.

Supported By: NIH/RO1 MH064824
Keywords: 22q11 Deletion Syndrome, Longitudinal, ADHD, Anxiety Disorders, Psychosis
466. Cortical Thickness Associated with Non-Suicidal Self-Injury and Impulsivity

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Background: Non-suicidal self-injury (NSSI) is the act of harming one’s own body tissue without suicidal intent. NSSI commonly begins in adolescence and is strongly associated with suicide (Victor and Klonsky 2014). Research is urgently needed to better understand neurobiological factors that contribute to the development and maintenance of this behavior. One way to understand potential neurobiological correlates is to examine cortical thickness within individuals with NSSI.

Methods: Twenty-eight females with NSSI and 22 healthy controls (HC) aged 13-21 completed a 3T structural MRI scan. We used the FreeSurfer tool QDEC to conduct cortical thickness analyses. Clinical measures included the Barratt Impulsiveness Scale (BIS; Patton et al. 1995) and the Difficulties in Emotion Regulation Scale (Gratz and Roemer 2004).

Results: Cortical thickness of the right lingual gyrus decreased with age in HC, but increased in NSSI (p<.005). Within the NSSI group, higher BIS scores were associated with lower cortical thickness in the left cuneus (p<.001) and right lateral occipital gyrus (p<.01).

Conclusions: Across the ages of 13-21, those with NSSI show a developmental pattern of cortical thickness within the lingual gyrus that differs from HC and typically developing females from previous research (Giedd et al. 1999). In NSSI, lower cortical thickness of the cuneus and lateral occipital gyrus was associated with greater self-reported impulsivity, which is consistent with prior research in bipolar disorder (Haldane et al. 2008). The present study adds to the limited existing research on the neurobiology of NSSI and may assist in our understanding of how to prevent and treat this behavior.

Supported By: NIMH 1R21MH094558; University of Minnesota Academic Health Center Faculty Research Development Grant Program; University of Minnesota Graduate School

Keywords: Non-suicidal self-injury, Cortical Thickness, FreeSurfer, Adolescents, Structural MRI

467. Childhood Adversity Linked to Lower Explicit Self-Esteem within a Mood Disorder Population

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Background: Significant research has been done to investigate the possible risk factors attributable to the development of mood disorders. Currently, neither childhood adversity nor self-esteem are systematically assessed among mood disorders patients yet these factors can play a role in assigning different types of treatment and in adherence to these treatment. To date, no study has examined explicit self-esteem in mood disorder patients who were previously exposed to childhood adversities (which include loss, neglect, antipathy, role reversal, physical abuse, sexual abuse, and psychological abuse). Aim: To examine the relationship between childhood adversity and explicit self-esteem in a mood disorder sample

Methods: For this cross-sectional study, 185 participants were recruited from the Mood Disorders Program of the McGill University Health Center in Montreal, Canada. Data was gathered using structured diagnostic interviews (SCID) and medical chart reviews. Childhood adversity was assessed with the Childhood Experience of Care and Abuse Questionnaire, which measures antipathy, parental loss, neglect, role reversal, and physical, psychological, and sexual abuse. Explicit self-esteem was measured using the Rosenberg Self-esteem questionnaire. Linear regressions were conducted to examine the association between specific types of childhood adversity and explicit self-esteem

Results: Parental antipathy was found to be associated with lower explicit self-esteem ($\beta = 0.268, p = .003$) in adult patients with mood disorders.
Conclusions: Childhood adversity, particularly parental antipathy, should be evaluated when assessing treatment options, patient adherence, and the overall prognosis of patients with a mood disorder. Psychotherapy targeted at improving self-esteem related parental antipathy should be considered.

Keywords: Mood disorders, Childhood Adversity, Self-Esteem

469. IL-10 is Associated with Increased Energy in Newly Arrived Traumatized Middle Eastern Refugees in the US
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Background: Post-traumatic stress disorder (PTSD) is a serious mental health problem that affects 7.8% of Americans. War-exposed persons have PTSD rates much higher. For example, veterans of the Gulf War conflicts have rates of PTSD as high as 40%. We still do not know what biomarkers are indicative of PTSD, which hampers the progress of mental health interventions. Refugees are an understudied population that can provide insight into the biological mechanisms of PTSD as well as mechanisms involved in resilience and resolution of disease.

Methods: Within the first month of arrival to the US, 60 male and female refugees from Syria were interviewed by an Arab-speaking research assistant using a validated, structured Arab-language survey that included questions about socioeconomic status, trauma, and toxin exposure. In addition to these questions they were given the DSM-IV PLC-C used clinically to diagnose PTSD. Blood samples were collected at the time of the interview and IL-1beta, IL-2, IL-6, IL-8, IL-10, and TNF-alpha, as well as kynurenine pathway metabolites measured by means of multiplex ELISA and GC-MS.

Results: Increased levels of the anti-inflammatory cytokine IL-10 in refugees correlated with higher energy levels (Pearson’s R, r=−.383, p<0.003). The ratio of TNF-alpha/IL-10, which is a tool to evaluate the balance between pro-inflammatory and anti-inflammatory cytokines, was inversely associated with refugees’ energy levels (Pearson’s R, r=−.468, p<0.003).

Conclusions: Overall this data suggests that IL-10 and the ratio of TNF-alpha/IL-10 could be important biomarkers of PTSD. Anti-inflammatory cytokines might be associated with increased energy levels; and potentially resilience and improved symptomatology in PTSD.

Supported By: R01; P30
Keywords: PTSD - Posttraumatic Stress Disorder, Inflammation, Interleukin, refugee, DSM-IV

470. Distinct Corticostriatal Structural Connectivity along the Bipolar Spectrum
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Background: The reward-sensitivity model of bipolar spectrum disorders (BSD) argues that risk for BSD is characterized by a hypersensitivity to reward. This hypersensitivity leads to an excessive increase in approach-related affect during reward pursuit, reflected in hypomanic/ manic symptoms. In line with this perspective, previous fMRI studies report abnormal reward-related neural activation in the medial orbitofrontal cortex (mOFC) and nucleus accumbens (NAcc). The present study extends this work by examining structural connectivity between mOFC and NAcc among individuals along a dimension of reward-sensitivity, including individuals with elevated reward sensitivity and a BSD.

Methods: Forty-Two participants from the Philadelphia area completed MRI scanning, the Behavioral Activation (BAS), and
diagnostic interviews. Participants were classified as moderate-BAS (n=13), high-BAS/no-BSD (n=18), and high-BAS+BSD (n=11). Structural images were automatically segmented in Freesurfer which generated bilateral nucleus accumbens (NAcc) and medial orbitofrontal cortex (mOFC) masks, which served as seeds for diffusion weighted probabilistic tractography. Fractional anisotropy (FA) was extracted from the probabilistic tracts.

**Results:** There was a significant group difference in structural connectivity between groups (F(1,41)=9.83, p<0.005). Moderate-BAS participants had significantly higher mOFC-NAcc structural connectivity compared to both high-BAS+BSD participants (t (1,23) = 2.64, p = 0.01) and high-BAS+BSD (t (1,23) = 3.76, p-value = 0.002).

**Conclusions:** Corticostratal structural connectivity is reduced along the bipolar spectrum, including among both individuals at risk for bipolar, as well as individuals with a BSD. Reduced structural connectivity in white matter connectivity between emotion generation regions (NAcc, mOFC) in a high risk population suggests that corticostratal connectivity may precede the first onset of BSD.

**Supported By:** 2T32MH067564, R01 MH100117-01, R01 MH077908-01A1

**Keywords:** Bipolar Spectrum Disorders, Structural Connectivity, Reward, Medial Orbitofrontal Cortex, Nucleus Accumbens

471. Resting Brain Connectivity Differentiates Suicidal Ideation from Acute Suicidal Behavior

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**Background:** Although several risk factors for suicide have been identified, it remains a clinical challenge to identify individuals at the highest immediate risk, with imminent need of acute medical intervention. Resting-state functional magnetic resonance imaging (rs-fMRI) is increasingly used to explore human brain-behavior relationships. We examined the value of rs-fMRI and multivariate pattern analysis to differentiate individuals who had attempted suicide in the last three days from those with less suicidal risk.

**Methods:** We recruited four groups of adults (n=54), ages 18–65 years: a) depressed patients who recently attempted suicide ( Attempters); b) depressed patients with suicidal ideation (Ideators); c) non-suicidal depressed patients; and d) healthy controls. Independent component analysis of rs-fMRI data was conducted with a reliable solution using 30 components. Twenty-one non-noise components corresponded to well-documented resting-state functional networks: default mode network (DMN), central executive, salience, limbic, occipital, somatosensory, and cerebellar networks.

**Results:** Using linear pattern classification modeling we were able to robustly differentiate Attempters from Ideators with 79% reliability (p = 0.0027), but not Attempters from the other depressed groups (p = 0.561), nor healthy controls from the three depressed groups (p = 0.112). A Haufe forward model of functional connectivity between the 21 components showed that connectivity of the DMN was markedly stronger in Ideators, while connectivity of the limbic network was stronger in Attempters.

**Conclusions:** The use of intrinsic brain activity to differentiate acute suicidal behavior from current suicidal ideation is a potential important step towards the development of a reliable and accurate biomarker of suicide risk.

**Supported By:** Translational Research Institute, grant UL1TR000039, National Center for Advancing Translational Sciences, Clinician Scientist Program of the University of Arkansas for Medical Sciences

**Keywords:** Suicide, Resting State, Inpatient, suicide attempts

472. Resting-State Functional Connectivity Dysfunction of the Ventral Striatum in Anhedonia as a Transdiagnostic Process

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**Background:** Anhedonia cuts across many neuropsychiatric disorders including depression, stress and addiction disorders. To develop more efficient treatments, we need to characterize the dysfunctions in the reward network that underlie significant loss of pleasure and positive affect independent of diagnostic labels. To address this issue, we examined MRI resting state functional connectivity aberrations associated with anhedonia in a clinical sample using a transdiagnostic approach.

**Methods:** Participants were recruited unfiltered by diagnosis and represented a broad spectrum of anxiety and mood-related symptoms. We acquired fMRI resting state data from 110 unmedicated participants at baseline as well as self-report measures of anxiety and mood symptoms, early life stress and other clinical measures. We focused on anhedonia defined by the anhedonia subscale scores of the Mood and Anxiety Symptom Questionnaire (MASQ) and on functional connectivity using a ventral striatal seed relevant to the reward circuit. We correlated anhedonia symptoms with functional connectivity of the ventral striatum while controlling for differences in general demographics, stress and anxiety symptoms, early-life stress, impulsivity, and emotion regulation and measures.

**Results:** Preliminary outcomes for whole-brain analyses indicate that the more severe anhedonia symptoms correlate with greater functional connectivity between the ventral striatum and an extended region on the left angular gyrus, relevant to the default mode network (voxel-level p = .001; cluster-level p = .005).

**Conclusions:** Hyper-functional connectivity involving regions of the reward and default mode circuits may contribute to more
severe anhedonia symptoms irrespective of psychiatric diagnosis. This association advances the characterization of a specific brain-based anhedonia phenotype.

Supported By: R01
Keywords: Resting state fMRI, Mood disorders, Anhedonia, Functional connectivity, Transdiagnostic

473. Failure to Downregulate Amygdala Activation during Regulation of Emotional Conflict in Post Traumatic Stress Disorder: Results from a Large Veteran Sample

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Background: Despite reports of aberrant amygdala activation in PTSD, the role of the amygdala in disordered emotional processing following trauma exposure remains unclear. We characterized amygdala activation during multiple emotional tasks in a large sample of trauma-exposed veterans.

Methods: Inside an MRI scanner, 73 combat-exposed veterans who met diagnostic criteria for PTSD and 51 asymptomatic combat-exposed controls completed tasks assessing emotional reactivity and interference resolution. We assessed task-based amygdala activation in each diagnostic group.

Results: We found no evidence of increased reactivity to emotional faces in PTSD patients relative to combat-exposed controls (p < .8), nor did either group show differential activation to fearful faces compared to sad or happy faces (each contrasted against a neutral-face baseline, p < .6). However, veterans with PTSD, compared to asymptomatic controls, failed to downregulate amygdala response to emotional faces during adaptive interference resolution (left, p = .006, Cohen’s d = .514; right, p = .025, Cohen’s d = .412). This effect was largest in patients with comorbid traumatic brain injury (N = 33, Cohen’s d = .655) and increased with severity of early (pre-military) trauma (Cohen’s f = .120, p = .008).

Conclusions: In contrast to previous reports, we found that the amygdalae of veterans with PTSD were not overreactive to emotional stimuli. Instead, PTSD patients responded normally to emotional stimuli, but failed to adapt to repeated exposure by downregulating this initial response during a cognitively demanding task. Implications for theories of PTSD as a disorder of emotional hyperarousal, and of disordered fear extinction, are discussed.

Supported By: Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress and Traumatic Brain Injury; Veterans Administration Palo Alto (MIRECC)
Keywords: BOLD fMRI, PTSD - Posttraumatic Stress Disorder, Emotion Regulation, Emotional reactivity, Replication

474. Effects of Left versus Right Dorsolateral Prefrontal Cortical Transcranial Magnetic Stimulation on Affective Flexibility in Healthy Women

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Background: The antidepressant mechanism of action for repetitive transcranial magnetic stimulation (rTMS) is not clear. Given the connectivity of the dorsolateral prefrontal cortex (DLPFC) target for rTMS within the cognitive control network (CCN), it is possible that rTMS may directly improve emotion regulation resulting in downstream antidepressant effects. We hypothesized that high frequency (HF) rTMS to the left but not right DLPFC would improve reappraisal of negative information using an affective flexibility task in healthy women.

Methods: Twenty-five (25) healthy females (mean age = 29.16 years; SD = 10.78 years) were randomized to left HF-rTMS versus right HF-rTMS in one session, then contralateral stimulation during a second session approximately one week later. Participants were not pregnant and had no major clinically significant psychiatric or neurological comorbidities. The affective flexibility task assessed switch costs in milliseconds for reappraisal of negative and positive information.

Results: A significant main effect of treatment side on reappraisal was found, F(1,19) = 6.145, p = .023. Specifically, participants’ ability to switch from an affective to a non-affective rule following presentation of negative information improved with rTMS applied to the left but not right DLPFC.

Conclusions: HF rTMS to the left but not right DLPFC improved ability to reappraise negative information in healthy women. These findings suggest left DLPFC HF rTMS may lead to antidepressant effects by directly improving emotion regulation. This suggests that successful treatment of TRD may act through strengthening DLPFC functioning and perhaps connectivity throughout this network.

Keywords: Repetitive Transcranial Magnetic Stimulation, Emotion Regulation, Affective Flexibility, Neuromodulation

475. Gender Differences in the Impact of Childhood Trauma on Impulsive Behaviors and Suicide Attempts in Pediatric Bipolar Disorder

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Background: Literature suggests that histories of childhood trauma (CT) leads to alterations of affect regulation and impulse
control, and is a risk factor for developing more severe forms of BD. While much is known about adult patients, there is limited data on that matter in pediatric BD (PBD). The present study addressed this issue by examining the link between CT, hostility, impulsivity, and affective liability in PBD.

**Methods:** Fifty nine PBD (Age: 13.76 ± 3.12 years; 30 girls), were administered the Childhood Trauma Questionnaire (CTQ), along with scales assessing emotional regulation, hostility, impulsivity, and suicide attempts. Data was analyzed using factorial ANCOVAs (factors: gender and CTQ scores; covariates: age, denial score, and number of traumas).

**Results:** Relative to boys without CT, those with physical or emotional abuse had greater severity of violence against property and punishment sensitivity (only for physical abuse), while it was comparable or lower for girls. Similar results were found for sexual abuse and physical violence and actual suicide attempts, in addition to a greater number of interrupted and actual suicide attempts in individuals with similar CT in general.

**Conclusions:** PBD boys with CT present externalizing behaviors such as suicidal and aggressive behaviors, and heightened punishment sensitivity. These findings support previous evidence of alterations in the brain inhibitory control networks in CT victims. Future large scale, longitudinal investigations are needed to determine whether externalizing behaviors appear much later in girls, and the extent to which they affect of the severity of the disease over time.

**Keywords:** Pediatric Bipolar Disorder, Childhood Trauma, suicide attempts, Aggression, Impulsivity

476. Molecular Insights of Dysregulated Microrna Network in Locus Coeruclus of Suicide Subjects

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**Background:** Norepinephrine (NE) is produced primarily by neurons in the locus coeruleus (LC). The core of the LC and its surrounding regions receive afferent projections from several brain areas which provide multiple neurochemical inputs to the LC with changes in LC neuronal firing making it a highly coordinated event. Although NE systems have been studied in relation to suicide, less is documented for corresponding changes in molecular network within LC. In this study, we examined miRNA networks in LC of depressed-suicide subjects and matched healthy controls.

**Methods:** miRNAs in LC of 9 suicide and 11 healthy controls were by analyzing by qPCR based array. SAM analysis was used to analyze significant differences in individual miRNAs. lgraph package in R was used analyze pairwise co-expression. The short listed target genes were analyzed with IPA for functional enrichment of target genes deciphering their role in canonical pathway, molecular network along with disease pathway using.

**Results:** A differential regulation of 13 miRNAs in LC of suicide brain was observed. Interaction between altered miRNAs and target genes showed dense interconnected molecular network, in which multiple genes were predicated to be targeted by the same miRNAs. Functional clustering of predicated target genes yielded stress induced disorders such as anxiety, hyperactive behavior, post traumatic disorders that collectively showed the complex nature of suicidal behavior. Also, a core set of 25 miRNAs was pairwise correlated with suicide group.

**Conclusions:** Our study for the first time reveal the involvement of LC based dysregulated miRNA network in disrupting cellular pathways associated with suicide.

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**Keywords:** Depression, Suicide, microRNA, Human Postmortem Brain, Epigenetic

477. A Biochemical-Connectivity-Psychological Model of Comorbid Depression in OCD: An Integrated fMRI/1H MRS Study

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UCLA

**Background:** Comorbid depression commonly occurs in obsessive-compulsive disorder (OCD), and is associated with worse functional impairment, poorer quality of life, and poorer treatment response. Understanding the underlying neurochemical and connectivity-based brain mechanisms of this important symptom domain in OCD is necessary for development of novel, more globally effective treatments.

**Methods:** Resting-state fMRI and 1H MRS data were obtained from participants with OCD (n = 49) and healthy individuals of equivalent age and sex (n = 25). Granger causality based effective (directed) connectivity was used to define causal networks of the right and left pregenual anterior cingulate cortex (pACC) as the reference seeds. The interplay between fMRI connectivity, 1H MRS and clinical data were explored by applying moderation and mediation analyses.

**Results:** We found that the causal influence of the right dorsal anterior midcingulate cortex (daMCC) on the right pACC was significantly lower in the OCD group (HC: 0.07 ± 0.008; OCD: 0.04 ± 0.006; p = 0.0130) and showed significant negative correlation with depressive symptom severity in the OCD group (r = -0.38, p = 0.008); those with weaker connectivity had higher depression severity. Lower and moderate levels of glutamate in the right pACC significantly moderated the interaction between right daMCC-pACC connectivity and depression severity.

**Conclusions:** In summary, we propose a biochemical-connectivity-psychological model contributing to comorbid depression in OCD, involving the right pACC, which has been previously implicated in depression and OCD symptoms. These findings have implications for potential molecular and network targets for treatment of this multi-faceted psychiatric condition.

**Supported By:** NIMH R01

**Keywords:** comorbid depression, OCD, resting-state fMRI, MRS, pregenual anterior cingulate cortex
478. An Interleukin-18 Haplotype Predicts Ventral Striatum Response to Positive and Negative Feedback in Young Adult Women but Not Men

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**Background:** A haplotype in the gene encoding interleukin-18 (IL-18), associated with higher expression of the pro-inflammatory cytokine IL-18, predicts increased risk of developing depression in response to stress. Given prior evidence that inflammation is associated with altered ventral striatum response to reward and punishment, we hypothesized that the IL-18 haplotype would be associated with individual differences in ventral striatum response to positive and negative feedback in a card guessing game associated with monetary reward in young adults.

**Methods:** Hypotheses were tested in 427 non-Hispanic European-American young adults who completed the Duke Neurogenetics Study. Participants were genotyped and underwent fMRI scanning while completing a card guessing task that included blocks in which they received positive feedback (indicating correct guesses) and blocks with negative feedback (indicating incorrect guesses), which they were informed was tied to monetary reward from the task.

**Results:** There was an interaction between IL-18 haplotype and sex, F(1,416)=4.13, p=.04, such that the IL-18 risk haplotype predicted higher ventral striatum response to both positive and negative feedback in women, but not men. Additionally, higher ventral striatum response to negative feedback was associated with higher depression symptoms in female participants, B=-7.33, Beta=-.15, p<.03.

**Conclusions:** These results indicate that, in women, a haplotype associated with increased IL-18 expression predicts higher ventral striatum sensitivity to both positive and negative feedback, and that ventral striatum sensitivity to negative feedback is associated with higher depression symptoms. Overall, ventral striatum response to punishment represents a potential pathway through which inflammation-related genotypes may influence risk for depression.

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**Keywords:** Ventral Striatum, Depression, Genotype, Inflammation, reward processing

479. Brain Complexity Changes during Stress Task in Patients with Major Depressive Disorder

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**Background:** Major depressive disorder (MDD) is a multidimensional disease characterized by abnormalities in the neurocircuitry underlying the stress response, mood appraisal, and affect regulation. Spontaneous brain activity is characterized by fractal-like temporal dynamics with long-range correlations in the BOLD signal, and measurement of nonlinear activation may provide a better understanding of brain complexity in disease and health (Sokunbi, 2016). The aim of the study was to use adaptive fractal analysis (AFA) and calculation of the Hurst exponent (H) to quantify dynamic properties of the BOLD time series for identifying differences between depressed patients from healthy volunteers.

**Methods:** Eighteen participants who met the DSM-IV criteria for current major depressive episode (average age 44.06, SD=9.66) and 10 matched healthy volunteers completed stressful and control math tasks during fMRI using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system. FMRI data were preprocessed using the AFNI package. Hurst parameters were calculated based on extracted time series from whole brain and region of interests (ROI) using AFA (Gao, 2010).

**Results:** Repeated measures ANOVA of average Hurst parameters from whole brain voxels showed no differences between groups. Mean Hurst exponent values from ROIs within the emotional network revealed a significant group effect (F=10.58, p=0.003), suggesting more coherent activation during both tasks in healthy participants, as well as a condition effect (F=17.815, p<0.001), higher H during stressful compared to control task.

**Conclusions:** Average Hurst exponent of the emotional network identified differences in dynamic properties of brain activation in subjects with MDD compared to healthy volunteers.

**Supported By:** This research was supported by grants from AstraZeneca, Inc and NIMH Award K23MH067705 to EBN and AAUW International Postdoctoral grant to AMK.

**Keywords:** Major Depressive Disorder (MDD), Stress, BOLD fMRI, Adaptive fractal analysis, Hurst exponent

480. Sex Differences in Emotional Perception: Meta Analysis of Divergent Activation

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**Background:** Behavioral and physiological sex differences in emotional reactivity are well documented, yet comparatively few neural differences have been identified

**Methods:** Quantitative activation likelihood estimation (ALE) meta-analysis examined functional brain imaging studies that each reported clusters of activity differentiating men and women as they participated in emotion-evoking tasks in the visual modality. This approach requires the experimental paradigm to be balanced across the sexes, and thus may provide greater clarity than previous efforts.

**Results:** Results across 56 emotion-eliciting studies (n = 1907) reveal distinct activation in the medial prefrontal cortex, anterior cingulate cortex, frontal pole, and mediodorsal nucleus of the thalamus in men relative to women. Women show distinct activation in bilateral amygdala, hippocampus, and regions of the dorsal midbrain including the periaqueductual gray/superior colliculus and locus coeruleus.

**Conclusions:** While some clusters are consistent with prevailing perspectives on the foundations of sex differences
in emotional reactivity, thalamic and brainstem regions have not previously been highlighted as sexually divergent. These data strongly support the need to include sex as a factor in functional brain imaging studies of emotion, and to extend our investigative focus beyond the cortex.

**Keywords:** Sex differences, Emotion perception, BOLD fMRI, Meta-analysis

481. Predicting Mood Disturbance Severity in Bipolar Subjects with Mobile Phone Keystroke Dynamics and Metadata

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1University of Illinois at Chicago, 2University of Michigan

**Background:** To demonstrate the feasibility of using mobile phone metadata to predict the presence and severity of mood disturbances in bipolar subjects.

**Methods:** For 8 weeks, 31 subjects with either bipolar disorder or no diagnosis were provided a mobile phone with a custom keyboard which collected metadata consisting of keystroke entry time, accelerometer movement, and use of backspace and space bar keys. Participants completed the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) weekly. Multiple linear regression models were created to predict the HDRS and YMRS scores of bipolar subjects who had provided 4 or more weeks of data (n=10).

**Results:** A statistically significant model for the prediction of HDRS scores was created (R-squared = 0.39). Four predictors were found to be significant (alpha < 0.05): ratio of backspaces to total characters, average length of typing sessions, average accelerometer movement, and total number of sessions. A model using these variables to predict YMRS scores was not found to reach significance.

**Conclusions:** It appears that changes in mobile phone usage as reflected in typing behaviors are significantly associated with changes in depression severity in bipolar subjects suggesting that passively collected metadata may be used to predict the presence and severity of depressive episodes. We speculate that models which include additional sensor data, semantic content, or are based on more flexible prediction methods may lead to further accuracy and precision. Analysis of the YMRS model showed violations of homoscedasticity and normality suggesting that effects of mania on keyboard dynamics may be more complicated.

**Keywords:** mobile health application, Bipolar Disorder, Predictive Analytics

482. Reduced Medial Prefrontal Functional Connectivity with Dorsal Anterior Cingulate Predicts Rumination and Negativity Bias in Late-Life Depression

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**Background:** Medial prefrontal networks, including the default mode network (DMN) mediate self-directed thoughts, including rumination and negative emotional bias (negativity bias), which are prominent features of depression. Recent studies suggest that the anterior part of the DMN is most affected in depression. We examined the relationship between rumination and resting state functional connectivity (RSFC) of anterior aspects of the DMN (anteromedial prefrontal cortex [amPFC]) in patients with late-life depression (LLD).

**Methods:** We examined 34 elderly depressed patients receiving escitalopram and 45 age and sex-matched controls (mean age = 72 ± 6.3 years). Rumination was measured using the Ruminative Response Scale. Resting state fMRI data was acquired during a 5-minute scan. Data processing involved motion correction, regression of covariates (white matter, CSF, 24 motion parameters, linear/quadratic trends), registration, smoothing (6mm), and filtering (0.01-0.1Hz), and RSFC was computed for a spherical seed (8mm radius) in mPFC. Group differences were thresholded at p = .001 voxelwise, p = .05 clusterwise.

**Results:** LLD showed a significant reduction in RSFC between amPFC and bilateral dACC compared to controls. We extracted the RSFC between the amPFC and bilateral dACC and examined correlations with rumination and emotional bias. Across groups, Total and Brooding Rumination scores correlated at r = -.44, p = .001. Moreover, higher amPFC/dACC functional connectivity was associated with both lower negativity bias (r = -.37, p = .009) and higher positivity bias (r = .34, p = .016).

**Conclusions:** The findings suggest that lower levels of rumination and negative emotional biases are related to reduced RSFC between amPFC and dACC. This suggests a neural circuit substrate through which escitalopram improves these factors.

**Supported By:** RO1 MH097735

**Keywords:** Resting state functional connectivity, Rumination, Geriatric Depression

483. Amygdala Response Predicts Clinical Symptom Reduction in Patients with Borderline Personality Disorder

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**Background:** Borderline personality disorder (BPD) is a prevalent, devastating and heterogeneous psychiatric disorder. Treatment success is highly variable within this patient group. Neurobiological mechanisms might mitigate phenomenological heterogeneity while also providing predictors of treatment success. Here we build on observations that BPD is accompanied by enhanced impact
of aversive affect on behavior and abnormal neural signaling in the amygdala. We assessed whether BPD is accompanied by abnormal aversive regulation of instrumental behavior and associated neural signaling, in a manner that is predictive of symptom reduction after therapy.

**Methods:** We tested a clinical sample of 15 patients with BPD, awaiting dialectical behavioural therapy (DBT), and 16 matched healthy controls using fMRI and an aversive Pavlovian-to-instrumental transfer (PIT) task that assesses how instrumental behaviors are influenced by aversive Pavlovian stimuli. Patients were assessed 1 year after the start of DBT to quantify changes in BPD symptom severity.

**Results:** At baseline, aversive PIT and associated neural signaling did not differ between groups. However, BOLD signal in the amygdala measured during aversive PIT predicted symptom reduction at 1 year follow-up: Enhanced aversive amygdala signaling before treatment was associated with reduced clinical improvement at follow-up.

**Conclusions:** Clinical symptom reduction over 1 year of treatment in BPD patients can be predicted from BOLD signal in the amygdala, measured using an aversive PIT task. This finding demonstrates a key role for the amygdala in the recovery of borderline personality disorder. Moreover, the results suggest that excessive responsiveness of the amygdala during aversive PIT might render patients resistant to symptom improvement.

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**Keywords:** Amygdala, Borderline Personality Disorder, Psychotherapy, fMRI, Translational research

484. Structural Relationships among the Revised Reward Sensitivity Theory and Grandiose and Vulnerable Narcissism

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**Background:** Studies examining the revised Reward Sensitivity Theory (RST) of personality in narcissism find inconsistent results. A better understanding of the RST and narcissism relationship can help inform future psychophysiological research. This study examines the contributions of the behavioral activation (BAS), behavioral inhibition (BIS), and fight-flight-freeze (FFFS) systems of the RST to narcissistic grandiosity and vulnerability. Based on previous research it was hypothesized that grandiosity would relate to elevated BAS and lower BIS and FFFS. Conversely, it was hypothesized that vulnerability would associate with greater BIS and FFFS.

**Methods:** Two geographically-independent samples of participants completed self-report measures of narcissism and the RST (N = 854; N = 258, respectively). A structural equation model (SEM) created in the first sample was well-supported and replicated with different narcissism measures in the second sample.

**Results:** SEM results indicated that grandiosity associated significantly with elevated BAS in sample 1 and 2 (standardized estimates [est.] = .46, .35, respectively). Vulnerability associated with elevated BIS across samples (est. = .51; .24). Grandiosity associated significantly with BIS (est. = –.28; –.06) and FFFS (est. = –.18; –.15) in sample 1 only; the same was true for vulnerability to the FFFS (est. = .17; .05).

**Conclusions:** Our data suggest that narcissistic grandiosity is characterized by approach motivation which may explain narcissistic admiration seeking. Vulnerability is associated with avoidance motivation which may be the result of a failure to receive the sought-for admiration. These results are consistent with contemporary clinical models of narcissism.

**Keywords:** narcissism, Reward, reward sensitivity theory, Structural Equation Modeling, behavioral activation & inhibition

485. Childhood Maltreatment and Normal Adult Personality Traits: Evidence for Developmental Sensitive Periods of Exposure

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**Background:** An association between childhood maltreatment and personality disorders is well documented in literature. However, considering that neuroticism is the most important and predominant trait underlying personality disorder symptomatology, we aimed to investigate a possible link between specific types and timing of abuse and its overall impact on normal adult personality traits, with an emphasis on sensitive exposure periods.

**Methods:** Our sample consisted of 119 subjects (39M/80F) between the ages of 18-19 years (mean age 18.98 ± 0.58). Subjects were interviewed (SCID) and severity and timing of exposure to ten forms of maltreatment were assessed using the Maltreatment and Abuse Chronology of Exposure (MACE) scale in addition to Traumatic Antecedents interview. Personality was assessed using 240 item Revised NEO Personality Inventory (NEO PI-R).

**Results:** Random Forest regression analysis (cforest) to calculate the maximal importance of exposure across age and type of maltreatment, revealed that Peer Emotional Abuse at age 14 was highly predictive of developing neuroticism (p<0.00025) along with its sub-facets (all p’s<0.001), while for agreeableness and it’s sub-facets, the strongest predictors were parental verbal abuse at age 10 (p<0.02) and non-verbal emotional abuse at age 11(p<0.006).

**Conclusions:** This study further supports the hypothesis that childhood maltreatment relates not only to maladaptive personality disorder traits but also to the ‘normal’ range of personality functioning. It also provides additional support for the hypothesis of developmental sensitive periods associated
with risk for psychopathology and furthers the evidence that certain types of maltreatment and the timing of exposure are crucial factors in development of psychopathology.

**Supported By:** NIDA R01 DA01784606

**Keywords:** childhood maltreatment, Personality, Personality disorder, neuroticism

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### 486. Longitudinal Recovery Trajectories of Patients with First Episode Psychosis

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**Background:** There is a large variability in the recovery trajectory of first episode of psychosis (FEP) patients. The goal of this study was to examine outcome differences among FEP patients using an unsupervised data driven clustering approach, and explore the diagnosis, cognitive function, and demographic characteristics of patients within each cluster.

**Methods:** A total of 129 FEP patients (93% anti-psychotic naive) with schizophrenia (SZ) (n = 82) or non-SZ psychoses (n = 47) were included in the baseline assessments and followed-up at 1-month, 6-months, and 1 year. The Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms, Wisconsin Card Sorting Test, and Neurological sign were used as predictors against Global Assessment of Functioning Scale (GAS) scores. We used an R package, K-means Longitudinal 3D (kml3d), to identify clustering trajectories and predict functional outcome.

**Results:** Four distinct functioning trajectories emerged: “poor”, “intermediate”, “good” and “catch-up”. Patients with the “good” outcome trajectory showed least baseline symptoms and were likely to be Caucasian, having higher SES and better premorbid functioning. Patients in the “poor” trajectory showed severe baseline symptoms and were more likely to be with SZ diagnosis, male, and having lower SES. Patients in the “catch-up” trajectory had severe baseline symptoms but were able to show good functioning recovery a year later. These patients were likely to be with SZ diagnosis, male Caucasian, and with low schizotypal personality disorder.

**Conclusions:** Patients at greatest risk of poorer recovery trajectories could be targeted for more aggressive treatment interventions to reduce function deterioration and improve recovery.

**Supported By:** NIHMH R01

**Keywords:** first episode psychosis, recovery trajectory, longitudinal, K-means clustering

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### 487. Clinical and Morphometric Predictors of Quality of Life at Three Year Longitudinal Follow up of a First Episode Psychosis Cohort

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**Background:** First episode psychosis (FEP) patients were followed up after a minimum of three years in order to determine the extent of progression of clinical and morphometric indices and their relationship with Quality of Life (QoL). While QoL has been explored with respect to clinical parameters, investigation into the role of brain regional deficits and QoL is less understood.

**Methods:** 45 FEP patients (18 non-affective psychosis) were recruited into the study and a proportion of these (n=32) underwent clinical and neuroimaging investigations 3 years later. Detailed clinical assessments were conducted including SCID, GAF, PANSS and QLS.

**Results:** To identify clinical and morphometric independent predictors of QoL at baseline, we used linear regression modelling. Lower quality of Life (QoL) was predicted clinically by higher baseline negative symptoms (t=−2.3, p<0.03) and improvement in negative symptoms (1.28, p<0.004) predicted higher QoL 3 years later. From a neuroimaging perspective, left lateral ventricular volume enlargement over the follow up period was predicted lower QoL (t=−2.29, p<0.03).

**Conclusions:** This study demonstrated that it was the trajectory of clinical and morphometric measures over time, particularly with respect to negative symptoms and left lateral ventricular volume respectively, that are most associated with QoL as an outcome measure. Such measures are likely to be markers of a neuroprogressive process that ultimately determines the functional outcome after the onset of psychotic illness.

**Supported By:** Health Research Board

**Keywords:** First-Episode Psychosis (FEP), Quality Of Life, Negative Symptoms, Longitudinal Brain Imaging, longitudinal cohort

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### 488. Sign-Tracking is Difficult to Extinguish and Resistant to Multiple Cognitive Enhancers

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**Background:** Sign-tracking is a type of Pavlovian conditioned approach (PCA) behavior that is thought to underlie some aspects of addictive behavior, due to evidence that sign-tracking is difficult to suppress or control, and that animals prone to sign-track also display more robust addiction-related outcomes such as cue-induced reinstatement of drug self-administration. We aimed to determine whether sign-tracking responses are resistant to extinction. We also tested whether extinction of sign-tracking could be facilitated by different classes of cognitive enhancers known to facilitate extinction of other learned behaviors.

**Methods:** We measured the effects of extinction training on a PCA procedure that exploits individual differences, such that...
identically trained rats developed one of three patterns of responses: sign-tracking (approach to the predictive cue), goal-tracking (approach to the location of reward delivery), or an intermediate response (both responses). We also compared the effects of systemic injections of three different cognitive enhancers on extinction of sign-and goal-tracking: sodium butyrate (a histone deacetylase inhibitor), D-cycloserine (an NMDA receptor partial agonist), and fibroblast growth factor 2 (a pro-synaptic neurotrophic factor).

Results: We found that, while goal-tracking extinguishes completely within four days, sign-tracking behavior persists for over three weeks during extinction training. None of the compounds we administered was able to facilitate extinction of sign-tracking.

Conclusions: These results indicate that sign-tracking is highly resistant to extinction training even when augmented with three classes of cognitive enhancers that are being investigated as pharmacotherapies for addicted patients. This work highlights one potential source of difficulty when attempting to control addictive behaviors.

Supported By: NARSAD Young Investigator Grant 20829; NIDA K08 DA037912-01

Keywords: Addiction, Pavlovian conditioning, Reinforcement learning, Individual differences, Instrumental learning

489. Examination of an Acute Role for Thyroid Hormone Regulation of Trauma-Related Plasticity and Memory Formation in the Amygdala

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Background: The thyroid hormone (TH) system has been associated with anxiety, depression and well implicated in early nervous system development. Despite this early progress, almost nothing is known about the potential role that the TH system may play in mediating synaptic plasticity within the amygdala that accompanies trauma exposure and underlies long-term traumatic memory formation.

Methods: Nonbiased RNA-sequencing and targeted qPCR was used to examine the regulation of genes in the amygdala in fear conditioned mice. Local amygdala infusions of triiodothyronine (T3) or the thyroid hormone receptor (TR) antagonist 1-850 were used to examine the role of TRs in fear memory consolidation and associated gene transcription. Additional studies employed overexpression of mutant TRs in the amygdala with accompanying molecular assays and fear conditioning behavioral tests.

Results: Nonbiased RNA-sequencing revealed dynamic regulation of seven TH related genes in the amygdala in response to trauma, (q<0.05). Targeted qPCR demonstrated a significant fear conditioning-related increase in TR-alpha and TR-beta mRNA in the amygdala compared to control animals (p<0.05). Behavioral experiments revealed that local TR inhibition impaired traumatic-fear memory consolidation (p<0.05) by affecting downstream trauma-associated gene transcription (p<0.05). Conversely, local amygdala infusions of T3 resulted in enhanced fear memory consolidation (p<0.05) and trauma-associated gene transcription (p<0.05).

Conclusions: We observed dynamic regulation of genes associated with the TH system in the amygdala at the time of trauma exposure. These data are the first of which we are aware to reveal a dynamic role for the TH system in mediating trauma response in the amygdala.

Supported By: Rappaport Mental Health Research Scholar Award (SAM)

Keywords: thyroid, amygdala, gene expression, trauma, memory

490. Ramelteon Improves Post Traumatic Stess Disorder-like Behavior Observed in FABP3 Null Mice

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Background: We recently reported that fatty acid binding protein 3 (FABP3, H-FABP) binds to the intracellular loop of dopamine D2L receptor and that FABP3 null mouse reveals dysfunction of dopamine-regulated motor coordination (J Neurosci 2010;30:3146; J Biol Chem 2014;289:18957). We here documented that FABP3 null mouse also exhibits an enhanced anxiety and impaired memory extinction like PTSD.

Methods: Wild type mice (C57BL6) and FABP3 null mice underwent fear conditioning once a day with consecutive 5 days and measured the fear acquisition and extinction for 35 days. When mice were administrated with melatonin receptor agonist, the drug was orally administrated once a day.

Results: The acquisition of contextual fear memory in FABP3 null was not distinguished from those in wild type mice. However, FABP3 null mice had deficits in extinction of contextual fear memory. For example, in one month after exposure to contextual stimulation, wild type mice significantly reduced the elapsed time until entering the chamber given footshock. The elapsed time remained elevated in FABP3 null mice, suggesting the deficits in the extinction. Likewise, the cFos expression in the amygdala after exposure to conditional contextual stimuli remained elevated in FABP3 mice but declined in the wild type mice at one month later. The administration of melatonin receptor agonist, ramelteon (1.0mg.kg, p.o.) completely improved PTSD-like behaviors in FABP3 null mice.

Conclusions: FABP3 null mice are novel model of PTSD, which is rescued by ramelteon.

Supported By: This research is partially supported by the Strategic Research Program for Brain Sciences from Japan Agency for Medical Research and Development, AMED.

Keywords: PTSD - Posttraumatic Stress Disorder, Anxiety Disorder, FABP, Ramelteon
491. Deficits in Docosahexaenoic Acid Accrual during Adolescent Development Reduces White Matter Microstructural Integrity in the Adult Rat Brain: An in Vivo Diffusion Tensor Imaging Study

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Background: Different psychiatric disorders that typically emerge during adolescence are associated with deficits in the long-chain omega-3 fatty acid docosahexaenoic acid (DHA) and regional deficits in brain white matter integrity (WMI). The present study determined the effects of dietary-induced alterations in cortical DHA accrual during adolescent development on WMI in the adult rat brain by diffusion tensor imaging (DTI).

Methods: From P21-P90 male rats were fed a diet with no n-3 fatty acids (Deficient, DEF, n=20), a diet fortified with preformed DHA (fish oil, FO, n=20), or a control diet (n=20). On P90 DTI data were acquired using a 7T Bruker Biospec system, and analyzed using region-of-interest and tract-based spatial statistics. Postmortem cortical and red blood cell fatty acid composition was determined.

Results: Compared with controls, PFC and RBC DHA levels were significantly lower in rats fed the DEF diet and significantly higher in rats fed the FO diet. In the corpus callosum, rats fed the DEF diet exhibited greater radial diffusivity (p=0.04) and medial diffusivity (p=0.04) compared with CON rats. Rats fed the DEF diet also exhibited greater radial diffusivity (p=0.01) and medial diffusivity (p=0.04) in the right external capsule compared with CON rats. Rats fed the FO diet did not differ from CON rats.

Conclusions: Based on prior animal evidence that demyelination or dysmyelination are associated with elevated radial diffusivity, the present data suggest that deficits in cortical DHA accrual during adolescent development reduce myelin integrity in the adult rat brain.

Supported By: NIH/NIMH R01 MH107378

Keywords: Rat, DTI, Omega-3 fatty acids, White matter

492. Epigenetic and Behavioral Outcomes Associated with Early-Life Adversity

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Background: Epigenetics research continues to provide insight into the biological basis of gene-environment interactions and developmental trajectories. We have designed a rodent model to explore the ability of infant experiences with caregiver adversity (maltreatment) to produce epigenetic alterations in the brain, and have observed sexually-dimorphic epigenetic alterations. Here we begin to assess the impact of our maltreatment regimen on several realms of behavior and whether manipulating chromatin structure impacts these behaviors.

Methods: Infant rats were repeatedly exposed to adverse caregiving environments from postnatal day 1 to 7. One cohort of rats was used to assess adult depressive- and anxiety-like behaviors, fear-related behavior, cognitive performance, and maternal behavior. In a second cohort of animals, drug (zebularine) was administered to adult females for one week following parturition. Levels of aversive caregiving behavior were analyzed. In a third cohort of rats, drug (sodium butyrate or 5-aza) was administered daily to infants prior to exposure to adverse caregiving environments and methylation levels were analyzed.

Results: Exposure to adverse caregiving significantly impaired adult behavioral performance, with substantial differences between sexes. Pharmacological manipulation of DNA methylation improved maternal behavior of maltreated-females, and a demethylating agent at the time of maltreatment prevented the emergence of aberrant methylation.

Conclusions: Data demonstrate the ability of repeated exposure to brief bouts of adverse caregiving to impact the development of several behavioral domains. Further, data illustrate the ability of chromatin modifying agents to change outcomes associated with maltreatment. Results will be discussed in the framework of mechanisms and targets for interventions in early-life stress.

Supported By: The Eunice Kennedy Shriver National Institute of Child Health and Human Development (1R01HD087509-01) The National Institute of General Medical Sciences (1P20GM103653)

Keywords: Maltreatment, adversity, epigenetic, behavior

493. Improvement of Social Interaction and Cognition by Oxytocin for Autism-Like Behaviors in Valproic Acid-Exposed Rats

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Background: Cognitive dysfunction and impairment of communication and social interaction have been observed in autism spectrum disorders (ASD). It is well known that maternal exposure to valproic acid (VPA) increases a risk of fetal ASDs. We addressed the question whether ASD-like behaviors in maternal VPA-exposed rats is improved by the neuropeptide oxytocin (OXT).

Methods: Sprague-Dawley pregnant female rats weighting 200-230 g were received a single oral administration of 600mg/kg sodium valproic acid at E12.5. Litter sizes, pup body weights, and general health of the mothers and pups were unchanged by treatment. The experiments were performed on the male offspring at postnatal days 50.
Results: The maternal VPA-exposed male rats exhibited severe deficits of spatial reference memory and subject recognition in Y maze and novel object recognition tasks. The VPA-exposed rats also revealed impairment of social interaction. Then, we investigated the effect of OXT (12μg/kg, i.n.) on ASD-like behaviors of VPA-exposed rats. Chronic administration of OXT for 2 weeks rescued not only impairment of spatial memory and cognition but also improved social interaction in VPA-treated rats. Moreover, we demonstrated that OXT treatment significantly restored reduced numbers of parvalbumin (PV) positive neurons in the hippocampus, basolateral amygdala and medial prefrontal cortex of VPA-exposed rats.

Conclusions: Maternal VPA-exposed rats are useful animal models of ASD for development of novel therapeutics and OXT may be useful to improve both social interaction and cognition in ASD patients.

Supported By: This work was supported by KAKENHI 25293124 and 24102505 (KF) in Japan Society for the Promotion Science.

Keywords: Autism Spectrum Disorder, Social Anxiety Disorder, Oxytocin, PTSD - Posttraumatic Stress Disorder, Parvalbumin Neuron

494. Selective Expression of Mutant DISC1 in Purkinje Cells Increased Their Spontaneous Activity and Produced Cognitive Abnormalities Relevant to Autism Spectrum Disorders

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Background: Various structural and functional abnormalities of Purkinje cells (PCs) have been observed in schizophrenia and autism. Disrupted-In-Schizophrenia-1 (DISC1) and its variants have been associated with neurodevelopmental disorders. Purkinje cells (PC) are neurons with highest expression of DISC1 in the brain. In order to explore the role of DISC1 in cerebellar physiology and associated ASD-relevant behaviors, we generated a mouse model of inducible and selective expression of dominant-negative form of DISC1 (truncated mutant human DISC1) in PCs.

Methods: We measured the volume of the cerebellum and PC size and number in mice at postnatal day 21 and 150, and assessed the behavioral phenotype in male and female mice of 3–7 months of age using a series of tests relevant to schizophrenia and ASD. Immunocytochemistry, image analysis and electrophysiology experiments were also performed.

Results: Mutant DISC1 male but not female mice demonstrated normal social interaction, and deficient novel placement recognition. Mutant DISC1 mice had significantly more PCs with smaller soma (~1000 μm3) and significantly fewer PCs with larger soma (~5000 μm3) at P21 but not P150, probably, because of lower RNA level in PCs with mutant DISC1. Whole-cell patch clamp and loose patch recordings in brain slices found larger amplitude, increased frequency of mEPSCs and spiking in mutant mice.

Conclusions: Our findings indicate that mutant DISC1 might alter physiology of PC to lead to cognitive and social abnormalities in mice. This may have the potential to advance our knowledge of the role of DISC1 in maturation and function of the cerebellum related to neurodevelopmental disorders.

Supported By: 1F05MH097457-01

Keywords: Cerebellum, Purkinje cell, Autism Spectrum Disorder, DISC1, Mouse model

495. Disruption of Brain-Derived Neurotrophic Factor Production from Promoter I Causes Social Behavioral Deficits

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Background: Brain-derived neurotrophic factor (BDNF) modulates neuronal plasticity and cognition. The BDNF gene is composed of nine distinct promoters that drive production of ~20 splice variants that encode the same BDNF protein. In mice, disrupting BDNF production from promoters I or II, but not promoters IV or VI, enhances intermale aggression. Here, we investigated how loss of BDNF from promoter I affects other social behavioral phenotypes.

Methods: We tested transgenic mice in which BDNF production is selectively disrupted from promoter I (Bdnf-e1 mice; Maynard et al, 2016) on a battery of social behavior assays including three-chamber social approach, pup-directed aggression (PDA), and copulation with females in estrous. Data were analyzed using Student t tests or one-way ANOVA with Bonferroni post hoc tests.

Results: Bdnf-e1 males exhibited social behavioral deficits in all assays tested compared to wild-type (WT) controls. Unlike WT males, Bdnf-e1 males preferred a novel object as opposed to a novel mouse in the three-chamber social approach test (p<0.001). Bdnf-e1 males attacked foreign pups and estrous females significantly more than WT males during PDA and copulation tests (p<0.01 and p<0.05, respectively).

Conclusions: Disruption of BDNF from a single promoter causes decreased sociability and increased aggression towards pups and females. Taken together with previous data showing that Bdnf-e1 males exhibit heightened intermale aggression, our studies suggest that BDNF derived from promoter I plays an important role in regulating social interactions. These studies highlight BDNF as a key molecular player in modulating complex social behaviors such as aggression, reproduction, and parenting.

Supported By: LIBD
496. Mania Phenotype in Comorbid Alcohol Use Disorder

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Background: Comorbidity between bipolar mania and alcohol use disorder is a serious condition and an important public health concern due to high symptom severity, delayed diagnosis, and worse treatment outcomes. Few studies have attempted to identify differences in the clinical presentation. Here we utilized our newly discovered lateral hypothalamus kindled (LHK) rat mania model to examine phenotypic differences in mania phenotype in alcohol preferring rats (P rats) with and without concurrent voluntary ethanol consumption.

Methods: Stimulating electrodes were placed in the lateral hypothalamus of 16 male P rats and kindling took place over 3 consecutive days. Half of the animals (n=8) received water only; the other half (n=8) received two bottle choice of water and 10% ethanol(v/v). Kindling-induced manic-like behaviors (rearing frequency, grooming, feeding, and genital licking durations) were video recorded and quantified and compared between the two groups.

Results: As expected, alcohol P rats exhibited classic manic-like behaviors during kindling and the post-kindling intervals in all coded behaviors (p<0.0001). However, there was no significant phenotypic difference between alcohol drinking and water drinking P rats (n=8 each); except for grooming which showed a non-significant trend: rearing [F(1,14)=1.651, p=0.2], grooming [F(1,14)=4.313, p=0.056], feeding [F(2,28)=1.256, P=0.3] and genital licking [F(1,14)=2.221, p=0.15]. Analyzed by two-way ANOVA.

Conclusions: Our results suggest that mania induction in alcohol P rats is similar to our previous findings with Wistar rats and manic phenotype is the same absence of alcohol intake. Further work is needed to delineate brain circuit during individual manic-like behaviors under ethanol and water conditions.

Supported By: grant support from NIH/NIGRA CTSA KL2 (RR024151)

Keywords: Mania, Alcohol Use Disorder, Phenotype, Bipolar Disorder, DBS

497. Study of Behavioral and Antioxidant Effects of Minocyclin in Rats Submitted by Motherhood Animal Model Privation

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Background: Major depressive disorder (MDD) is considered a serious public health problem and it is estimated that 350 million people are affected worldwide. Minocycline, an antibiotic, has shown antidepressant properties in experimental and clinical studies.

Methods: The present study investigated the behavioral and antidepressant effects of minocycline in rats subjected to the animal model of maternal deprivation. To this aim adult Wistar rats were used; the rats were subjected to maternal deprivation protocol in the first 10 postnatal (PND) days. The maternal privation protocol was performed for 10 days after the first PND day by three hours/day. In adult life Wistar male rats deprived and no n-deprived (control) were divided into four groups. Mice were treated with minocycline (25 mg/kg) or saline for 15 days, and then subjected to forced swimming and open field tests 1hour after the last drug administration.

Results: Maternal deprivation induced depressive-like behavior; however, minocycline treatment reversed this alteration, without change locomotor activity. The lipid damage was increased in the hippocampus of deprived rats, and treatment with minocycline did not reverse this effect. The carbonyl protein levels increased in the amygdala and hippocampus of deprived rats, and the treatment with minocycline did not reverse this alteration. In non-deprived rats treated with minocycline there was a reduction in the protein carbonyl levels in the amygdala, hippocampus and NAc.

Conclusions: The amygdala, hippocampus and NAc. In conclusion, minocycline exerted antidepressant-like effects in maternally deprived rats, and these effects could be attributed, at least in part, to its antioxidant effects.

Supported By: CNPO

Keywords: oxidative stress, Antioxidants, Animal Model, Major Depressive Disorder

498. Acetylcholinergic Mechanisms of Depressive-Like Behaviors Induced by Seasonally Relevant Reductions in Active Photoperiod

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Background: Seasonal variations in day length influences switching between mood states in bipolar disorder (BD). Treatments maintaining photoperiod stability support a euthymic state. Pharmacological-induced increase of acetylcholine (ACh) using physostigmine increases depressive-relevant behavior in mice and depression in BD sufferers. These studies were designed to test the hypothesis that ACh signaling is necessary for expression of depressive-like behaviors following exposure to short-active photoperiod (SAP).

Methods: Experiment 1: C57BL/6 mice were pretreated with the AChesterase inhibitor physostigmine 30 minutes before forced swim task (FST) followed by the muscarinic ACh receptor (mAChR) antagonist scopolamine or the nicotinic ACh receptor (nAChR) antagonist mecamylamine. Experiment 2: mice were
housed in SAP (19H light : 5H dark) for 2 weeks before FST, where they received scopolamine or mecamylamine.

**Results:** Scopolamine (F(2,49)=5.3, p<0.01) and mecamylamine (F(2,52)=4.6, p<0.05) decreased FST immobility in mice pretreated with the physostigmine. Immobility was not decreased in mice pretreated with saline (F<1, ns). SAP increased immobility in two cohorts (F(1,70)=6.5, p<0.05; F(1,143)=4.3, p<0.05). In cohort 1, 0.03mg/kg scopolamine reduced immobility irrespective of photoperiod (F(1,70)=6.9, p<0.05). As per our a priori hypotheses, it was discovered that this effect was driven by reduced immobility in the SAP (p<0.05), not in normal active photoperiod (NAP; 12:12) mice. In cohort 2, this effect was driven by reduced immobility in the SAP (p<0.05), not in normal active photoperiod (NAP; 12:12) mice. In cohort 2, 0.56mg/kg mecamylamine slightly reduced immobility irrespective of photoperiod, but not significantly (F(1,143)=2.0, p=0.15). In combination, two ineffective doses of antagonist additively decreased FST immobility (F(3,142)=3.0, p<0.05).

**Conclusions:** These results support ACh neurotransmission in expression of depressive-like behaviors resulting from exposure to altered photoperiod. Future studies will use more direct manipulation of ACh in these conditions.

**Supported By:** 5R01MH104344-03, 5T32MH018399-30

**Keywords:** Bipolar, Seasonal Affective Disorder, acetylcholine, Circadian Rhythms, Photoperiod

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499. **Disrupted Activity in Prefrontal Microcircuits in a Mouse Model of Genetic Risk for Psychiatric Illness**

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**Background:** The prefrontal cortex (PFC) and the neurotransmitter dopamine have been centrally implicated in depression. In animal models, prefrontal neurons expressing dopamine D2 receptors (D2Rs) have reduced activity and regulate depression related behaviors. However, it is not known how genetic risk for developing depression influences the responses of prefrontal microcircuits to dopaminergic input.

**Methods:** We have developed a novel assay, using live brain slices to image patterns of neural activity in isolated prefrontal microcircuits. A virus expressing the fluorescent activity reporter GCaMP6 was stereotactically targeted to medial PFC (mPFC) in mice. Subsequently, live slices were cut and activity imaged simultaneously from 70-100 prefrontal neurons during a baseline period and after exposure to a D2R agonist (quipiroline, 10 μM).

**Results:** Mice expressing a truncated version of the human Disc1 gene are an established model of genetic risk for depression and psychosis. We find that in slices from control mice, mean network activity increases nearly 2-fold in response to D2R stimulation and this response is significantly blunted in Disc1 mutant slices. Using a cell-type specific approach we find that this effect is most prominent in a subcortically projecting deep layer network. We further find that the overall organization of network activity is disrupted in mutant mice, with a specific deficit in significant positive correlations between pairs of neurons.

**Conclusions:** This novel assay defines an unbiased approach to discovering prefrontal microcircuit processes potentially important in the pathophysiology of depression and other psychiatric conditions.

**Supported By:** 3R01MH100292 - 04W1 NIMH R01 Supplement

**Keywords:** Depression, Prefrontal Cortex, Dopamine, Microcircuits, calcium imaging

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500. **Fronto-Striatal Modulation of Anxiety-Like Behaviors**

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**Background:** Anxiety disorders are some of the most common mental illnesses. Existing pharmacological therapies do not help a substantial fraction of patients, however these disorders respond particularly well to cognitive therapy. The prefrontal cortex has long been implicated in cognitive control and anxiety-related behaviors, although the precise downstream circuits and cell types mediating prefrontal control of anxiety are poorly understood.

**Methods:** Here we use a combination of in vivo and in vitro optogenetic and electrophysiological methods to identify causal top-down prefrontal projections and postsynaptic targets that control anxiety-like behavior in mice.

**Results:** We found that optogenetic stimulation of medial prefrontal cortex (mPFC) projections to the dorsomedial striatum (DMS) had an anxiolytic effect in the elevated plus maze (n = 9 Channelrhodopsin-2 (ChR2) and n = 8 eYFP control animals; p = 0.0003). In acute brain slices, mPFC projection stimulation preferentially recruited striatal medium spiny neurons (MSNs) expressing the D1 type dopamine receptor. Directly stimulating these postsynaptic D1 MSNs was sufficient to recapitulate the anxiolytic effect of mPFC-to-DMS projection stimulation (n = 12 ChR2 and n = 20 control; p = 0.002). Moreover, stimulating this fronto-striatal pathway was sufficient to rescue pathological behavior in a genetic mouse model of increased anxiety-like behavior.

**Conclusions:** These results implicate a previously unexplored top-down pathway for anxiety control, and highlight a role for the DMS in modulating affective behavior in addition to its well-characterized role in motor and cognitive behaviors.

**Supported By:** R01, UCSF

**Keywords:** anxiety, obsessive-compulsive disorder, prefrontal cortex, striatum, optogenetics

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501. **Epigenetic Modifications of Stress-Relevant Genes as Peripheral Biomarkers of Treatment-Resistant Depression**

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¹University of Illinois at Urbana Champaign, ²Mayo Clinic, ³University of Illinois

**Background:** Mechanisms contributing to treatment resistant depression (TRD) are poorly understood. Identifying peripheral biomarkers will enhance mechanistic understanding of the disorder and establish targets for personalized treatment
502. Disrupting Protein-Protein Interactions of Neuronal Nitric Oxide in the Medial Prefrontal Cortex and Dorsal Hippocampus: Implications in Schizophrenia-Related Behaviors

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Background: Neuronal nitric oxide synthase (NOS-I) and its adaptor protein (NOS1AP) have repeatedly been associated with schizophrenia. NOS1AP competes with interaction between NOS-I and PSD-95, which has been hypothesized to contribute to schizophrenia-related phenotypes. Here we aimed to investigate the relevance of NOS-I/PSD-95-interaction in schizophrenia-related behaviors by viral overexpression of proteins disrupting this interaction.

Methods: We stereotaxically targeted the medial prefrontal cortex (mPFC) or dorsal hippocampus (dHpc) of adult C57Bl/6J mice (N = 5-10/group) using recombinant adeno-associated viruses expressing (1) NOS1AP, (2) NOS1AP396-503, (3) NOS-I1-133, (4) mCherry (control). Four weeks post-surgery, mice were tested for open field (OF) activity, prepulse inhibition (PPI) of the acoustic startle response, and spatial working memory (SWM) on the T-maze. Results were analyzed by one-way ANOVA.

Results: We found no significant effect in OF (mPFC: F(3,16)= 1.102, p = 0.377; dHpc: F(3,16)=1.694, p = 0.186). PPI was mildly, but not significantly disturbed in mPFC (F(3,16)= 1.417, p = 0.274), but significantly affected in dHpc mice (F(3,16)= 3.854, p = 0.018). Post-hoc comparison revealed a significant PPI impairment only in NOS1AP mice (p = 0.042). SWM was mildly affected in mPFC mice (F(3,16)= 2.549, p = 0.092) with post-hoc comparison showing a significant SWM deficit in NOS1AP mice (p = 0.021) and a trend in NOS1AP396-503 (p = 0.077) and NOS-I1-133 (p = 0.051) mice. In dHpc mice SWM was significantly disrupted (F(3,16)= 4.602, p = 0.009), with post-hoc comparison showing a significant reduction for NOS1AP (p = 0.016), NOS1AP396-503 (p = 0.004) and NOS-I1-133 (p = 0.003) mice.

Conclusions: Our findings show an important involvement of NOS-I protein-interactions in phenotypes relevant for schizophrenia. Our results will eventually aid to a better understanding of NOS-I/NOS1AP-dependent psychopathogenesis and may lead to optimized treatment options.

Supported By: EC-FP7:602805 (AR); DFG:FR 3420/2-1 (FF)

Keywords: Nitric Oxide Synthase, Schizophrenia, Animal Behavior, Viral Gene Transfer, PDZ-interaction
samples from a large prospective Dutch military cohort at 6 months after a 4-month deployment period. Three polarized groups were selected: susceptible subjects with PTSD after trauma exposure, unsusceptible subjects without PTSD after trauma exposure and control subject without robust exposure to stress (n=8 per group).

**Results:** We identified differential expression of 32 microRNAs in the serum of susceptible persons and 15 microRNAs in the serum of unsusceptible subjects compared to controls.

**Conclusions:** Although further experiments need to be performed with more subjects, the results of our pilot study suggest that profiles of circulating microRNAs in human serum might provide biomarker candidates and possibly mechanistic information relevant to PTSD.

**Supported By:** EU grant Marie-Curie

**Keywords:** Post-traumatic stress disorder, Epigenetic, microRNA

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**504. Functional Single Nucleotide Polymorphisms in Human Trace Amine-Associated Receptor 1 Gene Impair Protein Kinase a Signaling Pathway for Amphetamine**

**Jingshan Chen,** Suzanne Underhill, and Susan Amara

NIMH, NIH

**Background:** The human trace amine-associated receptor 1 (hTAAR1) is a unique intracellular G-protein coupled receptor with high affinity for amphetamine, a potent drug for the treatment of attention deficit hyperactivity disorder (ADHD). The hTAAR1 plays an important role in the regulation of dopamine neurotransmission and may contribute to the anti-ADHD effects of amphetamine. We hypothesize that the genetic variations within the hTAAR1 gene may underlie the individual differences in response to amphetamine treatment. To test the hypothesis, we analyzed the effects of five single nucleotide polymorphisms (SNPs) in the hTAAR1 gene on amphetamine-induced protein kinase A (PKA) activation and dopamine uptake inhibition.

**Methods:** The wildtype and mutant hTAAR1 genes were cloned from human cell lines or generated by mutagenesis. The function of hTAAR1 in PKA activation was analyzed using a CRE-luciferase system. Dopamine uptake assays were conducted in HEK293 cells co-transfected with hTAAR1 and the dopamine transporter (DAT) genes.

**Results:** The R23C, S64F, R121C, T252A and N300K mutations abolished or dramatically decreased the amphetamine-induced PKA activation. The decrease in the T252A mutant-mediated PKA activation by amphetamine was not due to the loss of a potential phosphorylation site because a T252D mutation mimicking phosphorylation on the threonine did not rescue the hTAAR1 phosphorylation site because a T252D mutation mimicking PKA activation. The decrease in the T252A mutant-mediated PKA activation by amphetamine was not due to the loss of a potential phosphorylation site because a T252D mutation mimicking phosphorylation on the threonine did not rescue the hTAAR1 activation. All of the mutants no longer produced a decrease in DAT activity in the co-transfected HEK293 cells.

**Conclusions:** The five SNPs in the hTAAR1 gene are functional and could be used as genetic markers in the treatment of ADHD with amphetamine or other hTAAR1 agonists.

**Supported By:** NIMH Intramural Research Program

**Keywords:** Neuroendocrinology, Next Generation Sequencing, ESC/E(Z) complex, Mood disorders, Ovarian steroids

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**505. Lymphoblastoid Cell Lines from Women with Premenstrual Dysphoric Disorder Differ in Genetic, mRNA, and Protein Expression Profiles Compared with Asymptomatic Controls**

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**Background:** Premenstrual dysphoric disorder (PMDD) is characterized by recurrent affective and behavioral symptoms during the luteal phase of the normal menstrual cycle. Clinical studies show that in women with PMDD (but not controls), symptoms recur after re-exposure to physiologic levels of ovarian steroids (OS) during GnRH-agonist-induced ovarian suppression. These findings suggest abnormal cellular responsivity to OS.

**Methods:** To identify altered cellular pathways underpinning differential hormonal sensitivity, we created lymphoblastoid cell cultures (LCLs) from women with PMDD and asymptomatic controls. LCLs from cases and controls (n = 10, 9, respectively) were grown for 5 days, were either untreated or exposed to estradiol or progesterone (24 hours), and examined for differences in gene expression and protein via RNA-sequencing and ProteinSimple, respectively. Whole exome sequencing (Ion Torrent, Ampliseq) was performed on women with and without PMDD (n=52, n=27, respectively), then compared against each other and allele frequencies in ExAC.

**Results:** RNA-seq showed increased baseline expression in the ESC/E(Z) complex in PMDD, MTF2, PHF19, and SIRT1 (p<0.05) reaching significance, while protein analysis revealed opposite expression, MTF2, PHF19, and SIRT1 reaching significance (p<0.05). Exome sequencing (52x coverage total) identified functional variants in 11 genes in PMDD (p<0.05) versus controls, including NEFH, thought to play a role in neuronal intracellular transport.

**Conclusions:** Women with PMDD have ESC/E(Z) complex dysregulation at baseline and in response to OS, which could serve as the cellular basis for the differential behavior response to hormones observed in PMDD. We are integrating genome-wide chromatin and miRNA PMDD datasets to further these analyses.

**Supported By:** NIMH project MH002865; NIAAA project AA000301

**Keywords:** Neuroendocrinology, Next Generation Sequencing, ESC/E(Z) complex, Mood disorders, Ovarian steroids

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**506. Cyclic Expression of Circadian Genes in Neural Progenitor Cells Derived from Human Induced Pluripotent Stem Cells**

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NIH/NIMH/Human Genetics Branch

**Background:** Induced pluripotent stem cell (iPSC) technology has enabled the derivation of human neural progenitor cells...
(NPCs) that display circadian rhythms. Patient-derived NPCs may model some of the circadian disturbances that often underlie bipolar disorder (BD) and other mood disorders, but are difficult to study in humans. Using NPCs derived from a patient with BD and a healthy control, we investigated cyclic expression patterns of several genes known to participate in the canonical mammalian clock system.

**Methods:** Fibroblasts were reprogrammed with Sendai virus. Pluripotency was demonstrated by immunohistochemistry and fluorescence-activated cell-sorting. Karyotypically normal iPSCs were differentiated into NPCs, which were synchronized with forskolin and harvested at 6-hour intervals over 36-42 hours. Total RNA was extracted and reverse-transcribed into cDNA. Expression of RORA, PER3, CLOCK, SMARCD3 (BMAL1a), CSNK1D, and CSNK1E was assessed by qPCR. Using ARSER, expression was analyzed by harmonic regression based on autoregressive spectral estimation, yielding estimates of period, amplitude, phase, and statistical significance of any deviation from random oscillation.

**Results:** Several of the studied genes displayed significantly non-random oscillations of expression in NPCs (p<0.05). RORA, CSNK1E, and CSNK1D had the highest mRNA expression levels, with estimated periods close to 24 hr. In CSNK1D, BD NPCs had a period of 24.8 and a phase of 13.1 while control NPCs had a period of 27.6 and a phase of 17.0.

**Conclusions:** Human iPSC-derived NPCs display cell-autonomous, circadian expression of genes involved in the canonical circadian clock, providing a potentially valuable experimental system for the investigation of circadian biology in a variety of neuropsychiatric disorders.

**Supported By:** Supported by the Intramural Research Program of the National Institute of Mental Health, NIH.

**Keywords:** iPSC, Gene Expression, Circadian Rhythms, Neural Progenitor Cells, Bipolar Disorder

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**507. Association of NRXN3 Deletion with Schizophrenia and Bipolar Disorder**

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**Background:** Schizophrenia (SZ) and bipolar disorder (BD) are the most severe neuropsychiatric disorders affecting 1.2% and 4.4% of Americans, respectively. Certain genes coding for proteins involved in pre-synaptic machinery are thought to play a role in the pathophysiology of the disorder. Deficits in the calcium channel regulator gene NRXN3 have been associated with behaviors of impulsivity and alcohol and drug dependence, which are traits characteristic of BD and SZ.

**Methods:** In this study, we performed a family-based association analysis to determine if an 8KB deletion within the NRXN3 gene was associated with SZ, BD, or a combined phenotype in Latino populations. 2592 Latino individuals were genotyped using a TaqMan (Applied Biosystems, Foster City, CA, USA) in addition to standardized z scores and confidence values. Family based association testing was performed using the FBAT ver 2.0.4 software package for BD, SZ and combined phenotypes.

**Results:** SZ, BD, or combined phenotypes were not significantly associated with the NRXN3 deletion (p-value > 0.05).

**Conclusions:** Although we were unable to report a significant association between the NRXN3 deletion and BD, SZ, or combined phenotypes, a trend toward significance was seen in the BD (P=0.11) and combined phenotypes (P=0.13), most likely attributed to the BD phenotype.

**Keywords:** Schizophrenia, Bipolar Disorder, NRXN3

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**508. Perturbations in the Apoptotic Pathway and Mitochondrial Network Dynamics in Peripheral Blood Mononuclear Cells from Bipolar Disorder Patients**

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**Background:** Bipolar disorder (BD) is a potentially psychiatric disorder characterized by phasic changes of mood and can be associated with progressive structural brain change and cognitive decline. Because the dynamic morphologic changes of mitochondria are closely associated with the
initial process of apoptosis and the specific processes of apoptosis and mitochondrial dynamics in BD have not been fully elucidated, we measured the apoptotic pathway and the expression of mitochondrial fission/fusion proteins from BD patients and healthy controls.

**Methods:** 16 patients with BD-I and 16 age- and sex-matched healthy controls were recruited from outpatient clinics at the University of Texas Health Science Center at Houston. Human blood samples were collected in heparin collection tubes. Then, PBMCs were separated using LeucoPREP brand cell separation tubes, and intrinsic pathway of apoptosis, and the expression of mitochondrial fission/fusion proteins was assayed.

**Results:** Our results showed that the levels of the anti-apoptotic proteins Bcl-xL, survivin and Bcl-xL/Bak dimer were significantly decreased, while active caspase-3 protein levels were significantly increased in PBMCs from BD patients. Moreover, we observed the down-regulation of the mitochondrial fusion-related proteins Mfn2 and Opa1 and the up-regulation of the fusion protein Fis1 in PBMCs from BD patients.

**Conclusions:** The data reported here are consistent with the working hypothesis that apoptosis may contribute to cellular dysfunction, brain volume loss and progressive cognitive in BD. Moreover, we show an important relationship between mitochondrial dynamics and the cell death pathway activation in BD patients, supporting the link between mitochondrial dysfunction and the pathophysiology of BD.

**Keywords:** Bipolar Disorder, Depression, Mitochondria, Apoptosis, Mitochondrial dynamics

509. EGR3 in Bipolar Disorder: Preliminary Results of an In Vitro Study for Validation of Bioinformatics Findings

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**Background:** Using network-based approaches, we have previously shown that the regulatory unit of early growth response gene 3 (EGR3) is robustly repressed in postmortem prefrontal cortex from patients with bipolar disorder (BD). Accordingly, EGR3 regulates genes that mediate critical neurobiological processes, and seems to be related to brain-derived neurotrophic factor (BDNF). In this study, the aim was to characterize the gene expression profile of the human neuroblastoma differentiated SH-SY5Y cell line to evaluate whether this in vitro model would be appropriate to study the EGR3 regulatory unit.

**Methods:** Neuronal differentiation of SH-SY5Y cells was induced by retinoic acid for seven days, as well as with BDNF from the fourth day of protocol. Then, RNA was isolated and purified for microarray analysis (GeneChip PrimeView, Affymetrix). Differential expression and gene set enrichment analysis were performed to identify biological process associated with cell phenotypes and modulation of EGR3 by differentiation.

**Results:** Microarray data were deposited on GEO repository (GSE71817). Genes associated with the differentiated SH-SY5Y cells were related to synapse, regulation of neurotransmitter levels and membrane potential. EGR3 was associated with differentiated cells, mostly in response to BDNF.

**Conclusions:** We characterized the gene expression profile of differentiated SH-SY5Y cells reinforcing the neuronal phenotype of this in vitro model. Additionally, our results demonstrated that EGR3 is enriched in differentiated cells, suggesting that this regulatory unit is modulated by the differentiation process and induced by BDNF. This experimental model seems to be suitable for studying findings related to EGR3, which reveals new avenues to study BD.

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**Keywords:** Bipolar Disorder, EGR3, BDNF, SH-SY5Y cells, in vitro model

510. Major Depression, Childhood Trauma, Parenting Styles and Oxidative Stress: A Well-controlled Study in Unmedicated Individuals

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**Background:** Childhood trauma (CT) and major depressive disorder (MDD), are associated with increased risk for developing serious medical illnesses, although the causes of this are unknown. CT and MDD have been associated with oxidative stress, which could mediate these relationships, though this has not been well-studied, especially in somatically-healthy, unmedicated individuals.

**Methods:** Oxidative stress (F2-isoprostanes) and CT (Childhood Trauma Questionnaire [CTQ]) were assessed in 47 medically-healthy, unmediated adults with moderate-severe MDD and 55 healthy controls. As quality of parental upbringing may moderate the effect of childhood trauma on certain measures, parenting styles (Parental Bonding Inventory [PBI]) were also assessed. Analyses covaried for age, sex, BMI, and tobacco use.

**Results:** Compared to controls, MDD subjects had significantly higher F2-isoprostane levels (p = .012) and CTQ scores (p < .001), and poorer parenting styles (PBI Care and PBI Overprotection, all p-values < .001) than controls. Across subjects, F2-isoprostanes were correlated with CTQ (r = .248, p = .012), but not within each group. Within MDD only, F2-isoprostanes were positively trending with total CTQ scores (p = .095). In the whole sample, parental care was inversely correlated with F2-isoprostanes (p = .035), but not within groups.

**Conclusions:** Depressed individuals had higher F2-isoprostane levels and childhood trauma, and poorer parenting styles than well-matched controls. Across groups, greater childhood trauma and poorer parenting experiences were associated with greater oxidative stress. These are the first data in healthy unmedicated individuals, using appropriate stastistic controls for confounding factors, to demonstrate that childhood adversity is associated with oxidative stress, which may contribute to the development of adverse medical outcomes and may suggest novel targets for intervention.
511. Stress-Induced Neuronal CSF1 Provokes Microglia-Mediated Dendritic Remodeling and Depressive-Like Behavior

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Background: Chronic stress exposure causes pyramidal neuron dystrophy and synaptic deficits in the medial prefrontal cortex (PFC), which leads to development of anxiety-and depressive-like behaviors. Concomitantly microglia in the PFC undergo morphological and functional changes following stress exposure, suggesting that microglia contribute to stress-induced synaptic deficits underlying behavioral consequences.

Methods: Male and female mice were exposed to chronic unpredictable stress (CUS) to examine the effect of neuron-microglia interactions on synaptic deficits in the medial PFC. Thy1-GFP-M were used to assess microglia-mediated dendritic remodeling and spine density of pyramidal neurons in the medial PFC. Studies using viral-mediated knockdown determined the role of neuronal colony stimulating factor-1 (CSF1) in modulating microglia function and anxiety- or depressive-like behaviors after CUS.

Results: CUS promoted anxiety- and depressive-like behaviors that were associated with increased mRNA levels of CSF1 in the PFC. Increased CSF1 mRNA levels were also detected in postmortem dorsolateral PFC of depressed individuals. Moreover, frontal cortex microglia isolated from mice exposed to CUS show increased CSF1 receptor expression, morphological reactivity changes, and increased phagocytosis of neuronal elements. These functional changes in microglia corresponded with reduced dendritic spine density on pyramidal neurons in the medial PFC. Studies using viral-mediated knockdown determined the role of neuronal colony stimulating factor-1 (CSF1) in modulating microglia-mediated dendritic remodeling and prevented behavioral deficits caused by CUS.

Conclusions: These findings revealed that stress-induced elevations in neuronal CSF1 provoke microglia-mediated dendritic remodeling in the medial PFC, contributing to synaptic deficits and development of anxiety- and depressive-like behavior.

Supported By: NIMH grant MH82297, Animal Behavior core and Imaging Core of NIGMS grant P30GM103328

Keywords: Depression, Astrocytes, gap junctions, Sucrose Preference, Unpredictable Chronic Mild Stress

513. Functional Characterization of Ankyrin Loss of Function Mutations Associated with Autism Spectrum Disorder

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Background: Recent large-scale genomic studies have identified candidate genes involved in synaptic transmission that are highly associated with autism spectrum disorder (ASD), including ANK2 and ANK3. Loss of function missense mutations was associated with autistic patients. The goal of this project is to functionally characterize de novo loss of function mutations in ankyrins and identify their contribution to ASD.

Methods: A CRISPR/Cas9-based approach was used to transcriptionally repress ankyrin in a neuronal cell model. Fourteen sgRNA and one non-targeting control sgRNA were designed and screened for efficiency of transcriptional repression. Ankyrin levels were measured by qPCR. Tubulin polymerization and end-binding protein 3 expression were evaluated using Western blot. Furthermore, CRISPR/Cas9 was also used to induce point mutations within the Ank2 gene.
Results: Fourteen sgRNA were designed upstream of the transcriptional start site of exon 1b (Ank3b). Four sgRNA transcriptionally repressed Ank3b, however three of these had off-target effects. A single sgRNA had specificity for Ank3b and was located 139bp upstream from the transcriptional start site. Ank3b expression was reduced by 54% (p=0.03) after transcriptional repression. Repression of Ank3b increased the ratio of soluble:polymerized tubulin by 58% (p=0.02) indicating microtubule instability. The protein expression of end-binding protein 3 (EB3) was evaluated after transcriptional repression of Ank3b and resulted in a 20% increase in EB3 levels (p=0.02).

Conclusions: These results indicate transcriptional repression of ankyrin induces destabilizes microtubules which induces neuronal dysfunction associated with ASD. These data will provide a better understanding of the genetic factors underlying ASD.

Supported By: NARSAD, NINDS, NIMH

Keywords: ankyrin, Autism Spectrum Disorder, microtubules, CRISPR

514. Altered Protein Fucosylation in Schizophrenia Brain: Lectin Strategies to Identify Dysfucosylated Substrates

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Background: Our lab recently reported abnormal expression of fucose-modifying enzymes and reduced binding of Aleuria aurantia lectin (AAL) to α1,6-fucosylated N-glycopolypeptides, particularly in the ~52-58kDa and ~60-70kDa molecular mass ranges, in schizophrenia (SZ). The lectins Lens Culinaris agglutinin (LCA), Lotus Tetragonolobus lectin (LTL), and Ulex Europeaus agglutinin I (UEA-I) are known to bind specific fucose conformations with variable affinity. The specific fucosylglycan structures expressed and which protein substrates are adomed by fucosylglycan modifications in human brain are currently uncharacterized. In addition to α1,6-fucose, we hypothesize that multiple fucosylglycan structures are abnormally expressed in the disorder and are developing novel strategies to identify dysfucosylated substrates.

Methods: To determine patterns of lectin binding in human brain, we performed lectin blotting on cortical homogenates treated with or without deglycosylating enzymes Endoglycosidase H and PNGase F. To identify differences of lectin affinity in SZ brain, western blots of homogenates from SZ (N=16) and comparison subject (N=14) superior temporal gyrus (STG) were probed with biotinylated-LCA and streptavidin.

Results: Patterns of lectin binding demonstrate qualitative differences that indicate AAL, LCA, LTL, and UEA-I possess variable affinity for O-fucosylglycan and N-fucosylglycan structures in human cortex. LCA, similar to AAL, preferentially recognizes α1,6-fucosylglycans and LCA binding was found reduced in SZ [t(27)=2.09, p=0.04].

Conclusions: These data confirm our prior report of decreased α1,6-fucosylation in SZ STG. Additional studies investigating LTL and UEA-I affinity are underway. In order to characterize dysfucosylated protein substrates, lectin affinity capture methods are being optimized to enrich fucosylprotein targets for downstream mass spectrometric analysis and protein identification.

Supported By: MH53327

Keywords: Glycosylation, Human Postmortem Brain, Neuroglycobiochemistry, Core Fucose

515. Effects of PIK3CD Over-Expression on Neuronal Morphology: Implications for Schizophrenia

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Background: The PI3Kinase isoform, PIK3CD, has recently been implicated as a risk gene for schizophrenia. In addition to SNP associations in the PIK3CD gene locus, molecular work revealed elevated mRNA transcripts of PIK3CD in cells derived from patients with schizophrenia as compared to controls. While PIK3CD is expressed most abundantly in the immune system, recent work has begun to indicate a role for PIK3CD in CNS development and maintenance. Of particular import, PIK3CD inhibition can ameliorate behavioral phenotypes in rodent models of schizophrenia, supporting a role for PIK3CD in the brain and indicating PIK3CD could be an efficacious pharmaceutical target. Taken together, these findings highlight the importance of understanding PIK3CD function in the brain. To this end, we tested the hypothesis that increasing PIK3CD levels in neurons will result in morphological alterations consistent with phenotypes of schizophrenia.

Methods: We used a PIK3CD overexpression construct to transfect rat primary hippocampal cultures at different developmental time points and assessed subsequent effects on neuronal morphology.

Results: A sholl analysis revealed that temporally increasing PIK3CD levels decreased dendritic complexity (n=19,28; F=5.102, p<0.0005), which stemmed from both a decrease in dendrite number as well as length. Furthermore, PIK3CD overexpression increased dendritic spine density (n=45,39; t=−3.798, p<0.0005).

Conclusions: These morphological alterations are consistent with the altered signaling profile and morphometric changes of neurons in schizophrenia. Moving forward, we will build upon these results by further probing the PIK3CD pathway to assess effects on morphology and signaling as well as provide support for pharmacological inhibition of PIK3CD as a patient therapy.

Supported By: University of Colorado RNA Bioscience Initiative

Keywords: PIK3CD, Schizophrenia, p110delta

516. Omega-3 Fatty Acids Levels and ADHD Symptoms, Mood States, and Depression

Sophie Haven2, Rachel Gow2, Sharon Majchrzak-Hong2, James Loewke2, Yuhong Lin2, Reza Momenan2, and Joseph Hibbeln1

1National Institutes of Health, 2National Institute on Alcohol Abuse and Alcoholism

Results: Fourteen sgRNA were designed upstream of the transcriptional start site of exon 1b (Ank3b). Four sgRNA transcriptionally repressed Ank3b, however three of these had off-target effects. A single sgRNA had specificity for Ank3b and was located 139bp upstream from the transcriptional start site. Ank3b expression was reduced by 54% (p=0.03) after transcriptional repression. Repression of Ank3b increased the ratio of soluble:polymerized tubulin by 58% (p=0.02) indicating microtubule instability. The protein expression of end-binding protein 3 (EB3) was evaluated after transcriptional repression of Ank3b and resulted in a 20% increase in EB3 levels (p=0.02).

Conclusions: These results indicate transcriptional repression of ankyrin induces destabilizes microtubules which induces neuronal dysfunction associated with ASD. These data will provide a better understanding of the genetic factors underlying ASD.

Supported By: NARSAD, NINDS, NIMH

Keywords: ankyrin, Autism Spectrum Disorder, microtubules, CRISPR

514. Altered Protein Fucosylation in Schizophrenia Brain: Lectin Strategies to Identify Dysfucosylated Substrates

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Background: Our lab recently reported abnormal expression of fucose-modifying enzymes and reduced binding of Aleuria aurantia lectin (AAL) to α1,6-fucosylated N-glycopolypeptides, particularly in the ~52-58kDa and ~60-70kDa molecular mass ranges, in schizophrenia (SZ). The lectins Lens Culinaris agglutinin (LCA), Lotus Tetragonolobus lectin (LTL), and Ulex Europeaus agglutinin I (UEA-I) are known to bind specific fucose conformations with variable affinity. The specific fucosylglycan structures expressed and which protein substrates are adomed by fucosylglycan modifications in human brain are currently uncharacterized. In addition to α1,6-fucose, we hypothesize that multiple fucosylglycan structures are abnormally expressed in the disorder and are developing novel strategies to identify dysfucosylated substrates.

Methods: To determine patterns of lectin binding in human brain, we performed lectin blotting on cortical homogenates treated with or without deglycosylating enzymes Endoglycosidase H and PNGase F. To identify differences of lectin affinity in SZ brain, western blots of homogenates from SZ (N=16) and comparison subject (N=14) superior temporal gyrus (STG) were probed with biotinylated-LCA and streptavidin.

Results: Patterns of lectin binding demonstrate qualitative differences that indicate AAL, LCA, LTL, and UEA-I possess variable affinity for O-fucosylglycan and N-fucosylglycan structures in human cortex. LCA, similar to AAL, preferentially recognizes α1,6-fucosylglycans and LCA binding was found reduced in SZ [t(27)=2.09, p=0.04].

Conclusions: These data confirm our prior report of decreased α1,6-fucosylation in SZ STG. Additional studies investigating LTL and UEA-I affinity are underway. In order to characterize dysfucosylated protein substrates, lectin affinity capture methods are being optimized to enrich fucosylprotein targets for downstream mass spectrometric analysis and protein identification.

Supported By: MH53327

Keywords: Glycosylation, Human Postmortem Brain, Neuroglycobiochemistry, Core Fucose

515. Effects of PIK3CD Over-Expression on Neuronal Morphology: Implications for Schizophrenia

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Background: The PI3Kinase isoform, PIK3CD, has recently been implicated as a risk gene for schizophrenia. In addition to SNP associations in the PIK3CD gene locus, molecular work revealed elevated mRNA transcripts of PIK3CD in cells derived from patients with schizophrenia as compared to controls. While PIK3CD is expressed most abundantly in the immune system, recent work has begun to indicate a role for PIK3CD in CNS development and maintenance. Of particular import, PIK3CD inhibition can ameliorate behavioral phenotypes in rodent models of schizophrenia, supporting a role for PIK3CD in the brain and indicating PIK3CD could be an efficacious pharmaceutical target. Taken together, these findings highlight the importance of understanding PIK3CD function in the brain. To this end, we tested the hypothesis that increasing PIK3CD levels in neurons will result in morphological alterations consistent with phenotypes of schizophrenia.

Methods: We used a PIK3CD overexpression construct to transfect rat primary hippocampal cultures at different developmental time points and assessed subsequent effects on neuronal morphology.

Results: A sholl analysis revealed that temporally increasing PIK3CD levels decreased dendritic complexity (n=19,28; F=5.102, p<0.0005), which stemmed from both a decrease in dendrite number as well as length. Furthermore, PIK3CD overexpression increased dendritic spine density (n=45,39; t=−3.798, p<0.0005).

Conclusions: These morphological alterations are consistent with the altered signaling profile and morphometric changes of neurons in schizophrenia. Moving forward, we will build upon these results by further probing the PIK3CD pathway to assess effects on morphology and signaling as well as provide support for pharmacological inhibition of PIK3CD as a patient therapy.

Supported By: University of Colorado RNA Bioscience Initiative

Keywords: PIK3CD, Schizophrenia, p110delta

516. Omega-3 Fatty Acids Levels and ADHD Symptoms, Mood States, and Depression

Sophie Haven2, Rachel Gow2, Sharon Majchrzak-Hong2, James Loewke2, Yuhong Lin2, Reza Momenan2, and Joseph Hibbeln1

1National Institutes of Health, 2National Institute on Alcohol Abuse and Alcoholism
Background: Meta-analyses of randomized controlled trials (RCTs) report omega-3 fatty acids can reduce symptoms of attention deficit hyperactivity disorder (ADHD) in children. Here we present baseline data from a currently un-blinded RCT designed to evaluate efficacy in adults; the Neuroimaging, Omega-3 and Reward in Adults with ADHD trial (NCT02156089).

Methods: Thirty participants with ADHD aged 18-55 (M = 32.87, SD = 10.97, Female = 30%) were assessed using the Conner's Adult ADHD Rating Scales (CAARS) Self Report Long Version, the Profile of Mood States-Bipolar (POMS-Bi), and the Beck Depression Inventory (BDI). Concurrently, red blood cells were obtained to quantify fatty acid levels.

Results: Higher 22:6 n-3 (DHA) was associated with higher CAARS scores (r = 0.49, p < 0.006) and higher 22:5 n-6 was associated with lower CAARS scores (r = –0.42, p < 0.03). Higher 22:5 n-3 was associated with fewer depression symptoms (r = –0.41, p < 0.03) and higher levels of 20:2 n-6 (Eicosadienoic acid) was associated with greater depression symptoms (r = 0.51, p < 0.004). Higher 20:2 n-6 was positively associated with unsure (r = –0.49, p < 0.006), confused (r = –0.57, p < 0.001), depressed (r = –0.37, p < 0.05), and anxious symptoms (r = –0.52, p < 0.003).

Conclusions: The relationships between higher omega-3 and lower scores on the BDI at baseline are concordant with current literature on omega-3 and depression. Contrary to predictions, a positive association of DHA, and a negative association of 22:5n-6, with CAARS scores were found. Findings regarding 20:2n-6 are curious because this metabolic intermediate is not directly related to dietary intakes.

Supported By: Intramural Program of the National Institute on Alcohol Abuse and Alcoholism

Keywords: ADHD, Omega 3, Depressive symptoms, mood symptoms, Nutrition

517. Effects of Ketamine on Atypical and Typical Symptoms of Depression

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Background: Although ketamine has been shown to produce a rapid antidepressant effect, little has been reported regarding ketamine’s effects on subtypes of depression. Atypical depression, compared to typical (melancholic) depression, comprises a unique symptom cluster and may respond differentially to antidepressant treatments. We investigated whether atypical depressive symptoms, as measured by the Scale for Atypical Symptoms (SAS), improve after ketamine and if atypical symptoms improve more than typical symptoms, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS).

Methods: 68 subjects with treatment-resistant major depressive disorder (unmedicated) or bipolar disorder (on a therapeutic-dose lithium or valproate) were pooled across three double-blind, placebo-controlled, crossover studies investigating the efficacy of intravenous ketamine for depressive symptoms. Clinical symptoms were collected pre-infusion, and up to 14 days post-infusion, with effect sizes measured on days one and three post-infusion. Analysis of overall MADRS scores, SAS scores, and individual symptoms was performed in an exploratory manner.

Results: Overall MADRS (Cohen’s d = 0.55) and SAS (d = 0.33) scores demonstrated significant improvement one day post-infusion, with the most statistically significant (p < 0.05) improvements in MADRS individual items: pessimistic thoughts (d = 0.52), reported sadness (d = 0.47), and inability to feel (d = 0.45). On day three, MADRS reported sadness (d = 0.37), inability to feel (d = 0.36), concentration difficulties (d = 0.33), and apparent sadness (d = 0.33) demonstrated the most statistically significant individual symptom improvement. Overall MADRS (d = 0.43) and SAS (d = 0.33) scores continued to be significantly improved over placebo.

Conclusions: Although ketamine ameliorates both typical and atypical depressive symptoms, the effect size of ketamine over placebo was greater for typical symptoms one and three days post-infusion.

Supported By: ETPB, NIMH

Keywords: Ketamine, Treatment Resistant Depression, Major Depressive Disorder (MDD), Atypical Depression, Melancholic Depression

518. Patient and Clinician Acceptance of the Suicide Ideation and Behavior Assessment Tool (SIBAT)

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Background: Acceptance of new assessment tools by patients and clinicians who use them is important. The Suicide Ideation and Behavior Assessment Tool (SIBAT) has been developed to identify, track, and document suicidal ideation and behaviors in patients at risk for suicide. It has both patient-rated and clinician-rated components for clinical or research use. We demonstrate that this new instrument is acceptable to persons identified to be at risk for suicide and to their clinicians.

Methods: Fifteen adolescents with a history of suicide ideation and/or behavior in the prior month were consented to be interviewed using the SIBAT and then provide feedback on their experience with it. Likert scale and qualitative ratings were obtained. Following review of output from videotaped ratings of 3 patients with a varied range of symptoms, 16 clinicians rated their evaluation of each of the constituent modules for making global impression ratings. These clinician ratings were followed by telephone interviews to gain qualitative feedback.

Results: Patients rating for difficulty to understand, repetitiousness, burden, and offensiveness were low (mean changes were 1.5/5.0, 1.4/5.0, 1.1/5.0, and 1.0/5.0, respectively. Clinician ratings for the relative value of each of the SIBAT’s constituent modules for assessing global severity
varied from clinician to clinician. However, overall, clinicians found the instrument ‘valuable’ to ‘highly valuable’ as a clinical and research tool for making efficient, reliable assessments of suicidality and suicide risk.

Conclusions: This work provides strong support for patient and clinician acceptance of the SIBAT for suicide assessment.

Supported By: Janssen Research & Development, L.L.C., Raritan, NJ, USA

Keywords: depression, Suicide, suicide scale, patient-rated scale

519. Efficacy and Safety of Paliperidone Palmitate (3-Month versus 1-Month formulation) in European and Non-European Patients with Schizophrenia

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Background: To assess non-inferiority of paliperidone palmitate 3-month (PP3M) to PP 1-monthly (PP1M) formulation in patients with schizophrenia previously stabilized on PP1M, and compare efficacy and safety outcomes for European and non-European subgroups.

Methods: This randomized, double-blind (DB), multicenter, phase-3 study (EudraCT-2011-004889-15) enrolled patients of either sex (18-70 years) with schizophrenia (DSM-IV-TR), and a PANSS total score between 70 and 120. Patients previously stabilized on PP1M and treated with fixed-dose PP3M (175, 263, 350, or 525 mg eq. deltoid/gluteal) or PP1M (50, 75, 100, or 150 mg eq. deltoid/gluteal) for 48 weeks were included. Primary endpoint was percentage of relapse-free patients at the end of 48-week DB phase.

Results: Of patients who entered the DB phase, 498 (49.02%) were European (PP3M, n=253; PP1M, n=245) and 518 (50.98%) were non-Europeans (PP3M, n=251; PP1M, n=267). A similar percentage of patients in both groups (Europeans: PP3M, n=17 [7.4%]; PP1M, n=20 [8.4%]; non-Europeans: PP3M, n=20 [8.7%]; PP1M, n=25 [9.9%]) experienced a relapse during the DB phase. Kaplan-Meier estimate of difference (95% CI) between PP3M and PP1M in Latin American patients observed between PP3M and PP1M at Week 48 was -8.9%, 2.8%; i.e., the lower bound exceeded the pre-specified non-inferiority margin – 15%. The most frequently reported adverse event (>10%) was weight increased (26.5% PP3M, 16.2% PP1M), with mean weight increase (26.5% PP3M, 16.2% PP1M) in both groups in the percentage of patients who remained relapse-free at the end of DB were 1.0% (–4.3%; 6.2%) in Europeans and 1.4% (–4.4%; 7.1%) in non-Europeans. Incidence of treatment-emergent adverse events (TEAEs) was lower among Europeans (PP3M: 56.1%; PP1M: 59.2%) vs. non-Europeans (PP3M: 79.7%; PP1M: 73.0%). Weight gain was the most common TEAE across both subgroups.

Conclusions: PP3M was non-inferior to PP1M in both Europeans and non-Europeans. PP3M was generally tolerable and exhibited similar tolerability and efficacy in European and non-European populations.

Supported By: Janssen Research & Development

Keywords: Schizophrenia, Long acting injectable, Efficacy, European

520. Paliperidone Palmitate (3-Month Formulation) Administered Once Quarterly Prevents Relapse in Latin American Patients with Schizophrenia

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Janssen Research & Development, LLC

Background: Subgroup analyses of a double-blind [DB], active-control study [NCT01515423] were conducted to determine effect of paliperidone palmitate 3-monthly (PP3M) injection on relapse in adult patients with schizophrenia in Latin America (Argentina, Brazil, Mexico).

Methods: After screening (≥3 weeks) and 17-week, open-label phase (paliperidone 1-month formulation [PP1M] 150 mg eq. on day 1, 100 mg eq. on day 8, then 50-150 mg eq. every 4 weeks), 71 clinically stable patients (mean ± SD: age 41.2 ±12.32 years; age at schizophrenia diagnosis: 25.8 ± 8.35 years; 54% male) were randomized to fixed-dose PP3M (175, 263, 350, or 525 mg eq.) every 12 weeks or PP1M (50-150 mg eq.) every 4 weeks in a 48-week DB phase.

Results: One (of 34, 2.9%) patient in PP3M group and no patient (of 37) in PP1M group relapsed during the DB phase. Based on Kaplan-Meier analysis, 95% CI for difference in relapse-free rates between PP3M and PP1M at Week 48 was –8.9%, 2.8%; i.e., the lower bound exceeded the pre-specified non-inferiority margin – 15%. The most frequently reported adverse event (>10%) was weight increased (26.5% PP3M, 16.2% PP1M), with mean weight gain from DB baseline to endpoint of 1.7 kg and 2.8 kg in the respective groups. Two patients (5.9%) in the PP3M group and none in the PP1M group discontinued study drug prematurely due to an adverse event (anxiety, somnolence).

Conclusions: Overall, similar efficacy and tolerability were observed between PP3M and PP1M in Latin American patients with stable schizophrenia, which was consistent with observations globally.

Supported By: Janssen Research & Development, L.L.C.

Keywords: paliperidone palmitate, Schizophrenia, Relapse Prevention

521. Paliperidone Palmitate Improves and Maintains Functioning in Asia-Pacific Patients with Schizophrenia

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Background: Post-hoc analyses (2 open-label studies) were conducted to determine the impact of once-monthly injection of paliperidone palmitate (PP1M) on functioning in adult patients with schizophrenia in Asia-Pacific region.
Methods: Enrollment: Study 1, hospitalized patients with acute exacerbation of schizophrenia. Study 2, patients with recent-onset (≤5 years) schizophrenia unsatisfactorily treated with oral antipsychotics. Eligible patients received PP1M 150 mg eq. on day 1, 100 mg eq. on day 8, then once-monthly maintenance doses (50-150 mg eq) (Study 1: days 36 and 64; Study 2: 18 months). Functional status was evaluated by Personal and Social Performance (PSP) score in both studies and employment status in Study 2.

Results: In Study 1, 54/184 patients (29.4%) with an unfavorable level of functioning at baseline improved to favorable level (PSP score > 70) at day 92. Improvements were observed in all four PSP domains, including socially useful activities, personal and social relationships, self-care, and disturbing/aggressive behavior, significantly more so (p<0.05) for all domains, except disturbing/aggressive behavior, among those with recent-onset (≤5 years) compared with chronic (>5 years) schizophrenia. In Study 2, distribution of categorical PSP scores showed improvement, irrespective of baseline Positive and Negative Syndrome Scale score: 189/504 patients (37.5%) had PSP score >70 at week 5 and 275/507 (54.2%) at month 18. The proportion of patients fully/partially employed was greater at all post-baseline visits, as compared to baseline (134/280, 47.9% at month 18).

Conclusions: In post-hoc analyses, PP1M treatment led to prompt and sustained improvement in functioning among Asian patients with schizophrenia.

Supported By: Janssen-Cilag Asia-Pacific Medical Affairs, Beijing, People’s Republic of China

Keywords: paliperidone palmitate, Schizophrenia, Functioning, Atypical Antipsychotics, long-acting injection

522. The Difference in Clinical Outcome and Safety in Recent Diagnosis and Chronic Schizophrenic Disease after Paliperidone Palmitate 1 Month (PP1M) Treatment in Asian Patients

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Background: This post-hoc analysis explored the difference of clinical outcome and safety between recently diagnosed and chronic patients with schizophrenia after PP1M treatment in two clinical studies.

Methods: The primary analysis was to determine the difference between recently diagnosed and chronic subgroups measured by the change from baseline PANSS score. Key secondary analyses included differences in CGI-S scale score, and PANSS 30% responder rate.

Results: Study 1 (13 weeks) at 3 months, differences in mean (SE) PANSS scores (95% CI) were −2.30 (1.65) (p < 0.05) and −2.10 (1.58) (p < 0.05) at ≤5 years vs >5 years, respectively. Study 2 (18 months) at 1 year, differences in mean (SE) PANSS scores (95% CI) were −3.3 (1.6) (p < 0.05) at ≤2 years vs >2 years, ≤2 years vs >5 years, and >2 years vs >5 years, respectively. Differences in mean (SE) CGI-S scores (95% CI) at ≤2 years vs >2 years vs >5 years were −0.2 (0.10) (p < 0.05) and −0.2 (0.10) (p < 0.05) at ≤5 years vs >5 years, ≤2 years vs >2 years vs >5 years, and >2 years vs >5 years, respectively. Extrapyramidal and prolactin-related TEAEs were greater in chronic than in recently diagnosed schizophrenia.

Conclusions: Patients with recently diagnosed schizophrenia treated with PP1M had better outcomes than patients with chronic schizophrenia.

Supported By: Janssen Research & Development

523. Neurobiology of Extinguished Fear via Machine Learning

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Background: Neuroimaging research has identified brain regions that contribute to the pathophysiology of fear and anxiety disorders. We used machine learning to investigate whether activities of brain regions within the fear circuit could reliably distinguish healthy subjects from patients diagnosed with PTSD and anxiety.

Methods: 143 subjects (85 anxiety patients, 18 healthy controls, 14 trauma-exposed controls, 26 PTSD) were included in the study. Subjects underwent a two-day fear conditioning and extinction paradigm under fMRI. Activations from the ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex, amygdala, hippocampus, and insular cortex were recorded across all phases and subjects. A supervised machine learning approach combining evolutionary feature selection, neural network and boosted decision tree classification, and cross-validation was applied to identify neural signatures predictive of diagnostic outcomes.

Results: Multivariate ANOVA did not reveal statistical differences in activation between groups in any phase, and standard multivariate linear discriminant analyses produced poor classification accuracies (~50% in all comparisons). The supervised machine learning approach, however, resulted in correct classifications in 72.3% of subjects when comparing all four groups simultaneously and 82.4–93.8% of subjects when comparing pairs of groups. Furthermore, the models provided weighted contributions of each brain area to diagnostic accuracy. The most significant contributions were noted during extinction recall and within the vmPFC.

Conclusions: We show that the collective contribution of multiple brain regions across all phases of fear conditioning and extinction is central to discriminating fear- and anxiety-based disorders. These results provide evidence that machine learning can give neurobiological insight into the underlying dimensions of psychiatric disorders.
524. The Effect of Reward and Punishment on Inhibitory Control in Anxiety

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Background: Anxiety is associated with behavioral avoidance and inhibition that has been shown to influence cognitive control performance; however, it is not clear whether anxious individuals are less sensitive to reward or more sensitive to punishment when exerting self-control.

Methods: Participants high (n = 24) and low (n = 24) in trait anxiety (State Trait Anxiety Inventory) underwent functional magnetic resonance imaging while performing a Monetary Incentive Control Task. The task provided three reward outcomes contingent on inhibitory control performance over previously rewarded ‘go’ stimuli. Failure to inhibit a response to a ‘stop’ stimulus was followed by a monetary reward, a monetary loss or no monetary gain/loss. Each condition was signaled by a cue that appeared prior to stimulus presentation.

Results: Reaction times, accuracy and brain activation associated with anticipation (cue), stimulus and feedback were measured. Compared with the low trait anxious group, the high trait anxious group demonstrated reaction time slowing to go trials regardless of condition (p = .007). In the high compared to low trait anxious group, the left dorsal posterior cingulate cortex was more deactivated during reward anticipation and the right middle frontal gyrus was more activated during punishing feedback.

Conclusions: Participants high in trait anxiety maintained self-control over reward and avoided punishment by increasing cautious behavior. They slowed responses to potentially rewarding stimuli, suggesting that successful self-control required greater cognitive effort, consistent with patterns of neural activation showing greater cortical processing in cognitive control regions when anticipating reward, and more responsiveness to punishing feedback.

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Keywords: cognitive control, Anxiety, reward processing, punishment, Response inhibition

525. The Temporal Stability of Cognitive Functioning and Functional Capacity in Women with PTSD

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Background: In addition to clinical symptoms, patients with post-traumatic stress disorder (PTSD) often experience considerable disability and evidence deficits in cognition and functional capacity (FC).

Methods: In this study, assessments of cognition, functional capacity, and clinical symptoms were conducted over two time points in 96 women with PTSD to measure the temporal stability of performance on measures of cognition, functional capacity, and clinical symptoms. Intercorrelations between measures and consistency of these correlations over time were also assessed.

Results: Cognitive and FC deficits manifested temporal stability, beyond that of clinical symptoms in the current sample. FC deficits did not change over time. Results in these patients with PTSD were similar to those in patients with schizophrenia and bipolar disorder, indicating that measures of symptoms and self-reported disability are somewhat unreliable when used as indices of real world functioning or cognitive performance.

Conclusions: Self-reported disability was consistent with current symptomatology, but unrelated to objective measures of performance. Patients with prominent mood symptoms likely estimate their current level of functioning based on those symptoms. Future research into treatments that target cognition and improve real world functioning in PTSD is needed.

Supported By: U19 MH060906
Keywords: PTSD - Posttraumatic Stress Disorder, Cognitive skills, functional capacity, Women, Mental illnesses

526. New Methods for Assessing Hippocampal and Prefrontal Cortex Activation during Pattern Separation and Completion

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Background: Pattern Separation (PS) and Pattern Completion (PC) are memory processes dependent on hippocampal (hpc) - medial prefrontal cortex (mPFC) circuitry. These processes likely have relevance to fear learning in PTSD, as encoding and retrieval of contextual information is crucial to disambiguate potential threat cues. We are developing novel tasks to assess PS and PC of complex scenes in PTSD.

Methods: Healthy adults completed the following PS and PC tasks during fMRI: 1) the Mnemonic Similarities Task (MST) to assess PS and PC of complex scenes in PTSD. We propose to further utilize these tasks to test hypotheses regarding hpc and mPFC dependent potential threat cues. We are developing novel tasks to assess PS and PC of common objects (reliably activates hpc; Stark et al., 2013); 2) novel tasks currently under development in our lab to assess PS and PC of complex scenes.

Results: Preliminary findings (N = 13) replicate previous reports of hpc and mPFC activation during the well-established MST. We observed relationships between task performance and activation in vmPFC (−6, 56, 4) and hpc (18, −36, −5; 40, −13, −15) during PS. On one of our novel tasks (N = 9), we observed similar results in vmPFC (18, 50, −2) and hpc (−18, −22, −17) during PS. Significance thresholds were set at p < .005 uncorrected. Data collection is ongoing.

Conclusions: Though preliminary, our results replicate previously reported hpc and mPFC activity associated with PS and PC, and extend these findings to novel tasks examining PS and PC of complex scenes. We propose to further utilize these tasks to test hypotheses regarding hpc and mPFC dependent...
memory deficits that may underlie fear learning abnormalities in PTSD.

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Keywords: Memory, fMRI

527. Evaluating the Association between Neural Oscillations and Working Memory in Individuals with Mild Cognitive Impairment or Alzheimer’s Dementia

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Background: Working memory impairments are common in Alzheimer’s Dementia (AD) and some forms of mild cognitive impairment (MCI). Neural oscillations, specifically the modulation of gamma by theta oscillations - theta-gamma coupling (TGC) - represents a neurophysiological marker of working memory among healthy individuals. This study evaluated the association between neural oscillations and working memory performance in AD and MCI.

Methods: 33 participants with AD (Mean age = 76.5 ± 5.9; Mean education = 13.4 ± 3.7), 34 with MCI (Mean age = 74.7 ± 5.9, Mean education = 15.3 ± 2.3), and 30 healthy controls (HC) (Mean age = 73.5 ± 5.3, Mean education = 15.6 ± 2.4) were assessed using the N-back working memory task and electroencephalography (EEG) to measure TGC during N-back performance.

Results: After controlling for education, there was a group effect on 2-back performance (F(3, 88) = 30.4, p < 0.001) driven by the AD group who demonstrated lower accuracy compared to all others. In contrast, there was a group effect on TGC (F(3, 82) = 9.4, p < 0.001) driven by the AD group as well as the MCI group, both having lower coupling than controls. Finally, a linear regression demonstrated that TGC (β = 0.34, p = 0.003) and not theta (β = −0.10, p = 0.36) or gamma (β = −0.11, p = 0.34) power predicted 2-back performance.

Conclusions: Understanding the neurophysiologic mechanism that contributes to and predicts memory impairments in individuals at-risk for or with AD is a critical first step in guiding novel preventative interventions.

Supported By: Brain Canada

Keywords: Alzheimer’s Disease, EEG, Working memory, Neural Oscillations

528. Cognitive Ability is Related to White Matter Tract Integrity in 1-Year-Olds

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Background: Mounting evidence reveals white matter (WM) integrity as an indicator of cognitive ability in children and adults. However, it is unknown how WM fibers support cognitive development in early life. This study explores relationships between in-vivo WM microstructural properties and cognitive ability in the first year of life.

Methods: Tract-based diffusion properties (FA, RD, AD) were computed using diffusion tensor images (DTIs) from healthy neonates (n=158) and 1-year-olds (n=255). Cognitive measures at 1-year (COMP1) were collected using the Mullen Scales of Early Learning. Data were analyzed using two methods: one comparing local point-by-point tract properties, and another comparing global tract-average properties to COMP1.

Results: Lower local RD along corticofugal (CF) and corticothalamic (CT) tracts related to higher COMP1 (p<0.05). Higher local FA along the right SLF and arcuate also related to higher COMP1 (p<0.005). Both local and global RD at 1-year negatively related to COMP1, most significantly between CF and CT tracts, but also between the bilateral cingulum, right SLF, and left uncinate (local: p<0.05; global: p<0.001). 1-year tract-average results for AD overlap with RD, and positive associations between FA and COMP1 were found with the splenium and left inferior longitudinal fasciculus.

Conclusions: More mature microstructural properties along major WM bundles at birth and 1-year is related to future and present cognitive ability. Tracts detected as markers of early ability are important for primary sensory, sensory integration, and higher-order cognitive functions. Results from this study suggest WM integrity in early life is important for emerging cognition.

Supported By: HD053000, T32NS007431, T32HD07376

Keywords: White Matter Tractography, Diffusion Tensor Imaging (DTI), Brain Development

529. Reducing Impulsivity with Transcranial Direct Current Stimulation (tDCS) and a Cognitive Task

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Background: Impulsivity is a multidimensional construct that includes lack of premeditation, sensation-seeking, and impaired cognitive control. Impulsivity is observed clinically, and can manifest as poor decision-making and excessive risk-taking. Transcranial direct current stimulation (tDCS) applied over dorsolateral prefrontal cortex (DLPFC) has been shown to decrease risk-taking behavior. This study explores the effects of tDCS on risk-taking in participants who exhibit clinically-relevant impulsivity.

Methods: Participants complete two tDCS sessions per day for five days with additional one and two month follow-up sessions. Participants complete questionnaires and behavioral measures of impulsivity and risk-taking (e.g. Cued Reaching Task (CRT), Risk Task) pre- and post-intervention. Participants are randomly assigned to receive either active or sham tDCS
530. Transcranial Magnetic Stimulation Induced Brain Response in Major Depressive Disorder

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Stanford University

**Background:** Disturbances in the function of large scale brain networks has been implicated in Major Depressive Disorder (MDD), but the causal mechanisms underlying this network function remain uncertain. Transcranial magnetic stimulation (TMS) is a noninvasive method to causally modulate brain activation and an FDA approved treatment for depression. Despite this, there remains a limited understanding of how TMS affects brain networks in patients with major depressive disorder (MDD), which limits development of novel treatment targets. Posterior middle frontal gyrus (pMFG) is a key node in the executive control network that has been shown to causally inhibit activation in the default mode network (DMN). Dysregulated activation of DMN regions such as the ventromedial prefrontal cortex (VMPFC) has been related to deficits in emotional reappraisal, rumination, and depression severity, in patients with MDD.

**Methods:** Using concurrent TMS/fMRI to right pMFG, we compared TMS response in healthy controls (n=22) to that of unmedicated patients with MDD (n=23).

**Results:** We found significant group differences in pMFG TMS-induced activation in DMN regions including VMPFC and posterior cingulate (corrected for multiple comparisons). These results confirm that pMFG is causally involved in regulation of the default mode network in MDD.

**Conclusions:** These results replicate an endogenously observed dynamic in MDD patients during previous task and resting state studies for the first time using concurrent TMS/fMRI, and suggest that TMS can be used to probe brain circuitry differences that may underlie psychiatric disorders to inform novel treatment targets.

**Supported By:** BRAINS R01

**Keywords:** Transcranial Magnetic Stimulation, Major Depressive Disorder (MDD), BOLD fMRI, Default Mode Network, Executive Function

531. Effect of Antidepressant Treatment on Cognitive Impairments Associated with Depression: A Randomized Longitudinal Study

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**Background:** Antidepressant treatment failure is a common problem. We assess whether or not an important aspect of depression, cognitive impairment, is untreated by antidepressants.

**Methods:** In this randomized, open-label, prospective longitudinal study, part of the International Study to Predict Optimized Treatment in Depression (iSPOT-D) trial, we assessed the effects of acute antidepressant treatment in a large patient population, across clinical remission outcomes, on nine cognitive domains including several higher-order executive functions, memory, and processing and response speeds. Our primary outcome measure was cognitive change after eight weeks of treatment in depressed patients. We enrolled untreated outpatients (1008, aged 18-65 years) in a depressive episode and assessed for cognitive function at enrollment and again after eight weeks of treatment with one of three antidepressant drugs (escitalopram, sertraline, or venlafaxine extended-release, randomly assigned). We also enrolled matched healthy participants who received no medication, but were assessed using the same protocol, acting as a test-retest control. This study is registered with ClinicalTrials.gov, number NCT00693849.

**Results:** Impairment in five domains—attention, response inhibition, verbal memory, decision speed, and information processing—showed no relative improvement with acute treatment (controlling for time or repeated testing), irrespective of treatment group, even in patients whose clinical measures indicated remission. Broader cognitive impairment was associated with earlier illness onset.

**Conclusions:** Depression is associated with cognitive impairments which persist independently of clinical symptom change with treatment, across the three antidepressants tested. Although the eight-week treatment period limits interpretation to acute effects, it does highlight cognitive impairment as an untargeted contributor to incomplete treatment success.

**Supported By:** Brain Resource Company Operations Pty Ltd and NIH

**Keywords:** Major Depression, cognition, Antidepressant response, Clinical-Trial

532. Multimodal MRI Analysis of Medial Prefrontal Cortex and Cognitive Control in Adolescent Bipolar Disorder

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**Background:** Cognitive impairment is a hallmark of bipolar disorder (BD) and is associated with impairment in executive function and working memory. KD2515 is an antipsychotic approved for BD, but evidence of its effects on cognitive function is lacking. We assessed the effect of KD2515 on cognitive function in adolescents with BD using a randomized controlled trial (RCT).

**Methods:** This was a 12-week RCT of KD2515 in 34 adolescents (18-25 years) with a primary diagnosis of BD. The primary outcome measure was cognitive performance as assessed using the NimHSA cognitive battery, which was assessed pre- and post-treatment. We also assessed changes in regional brain volume and connectivity using voxel-based morphometry (VBM) and diffusion tensor imaging (DTI). Participants were randomly assigned to receive KD2515 or placebo.

**Results:** There was a significant increase in cognitive performance from pre- to post-treatment in the KD2515 group, but not sham, group. There were also significant increases in regional brain volume and connectivity in the KD2515 group, but not the placebo group.

**Conclusions:** KD2515 is effective in improving cognitive function in adolescents with BD, and this effect is associated with changes in regional brain volume and connectivity. These findings support the use of KD2515 as a potential treatment for cognitive impairment in BD.

**Supported By:** Canadian Institutes of Health Research (CIHR)

**Keywords:** Bipolar disorder, executive function, working memory, voxel-based morphometry (VBM), diffusion tensor imaging (DTI).
Background: Cognitive control deficits in bipolar disorder (BD) are debilitating and relatively unexplained. Our recent findings have implicated frontal medial prefrontal cortex (mPFC) in aberrant deactivation deficit during sustained attention, aberrant resting state functional connectivity (rsFC), and aberrant cerebral blood flow (CBF). Thus, the current study sought potential evidence for multimodal mPFC effects on cognitive control.

Methods: Adolescents (13-19 years; n=30 BD, n=20 HC) completed a Go-NoGo functional magnetic resonance imaging (fMRI) task. During the same session resting state fMRI, arterial spin labeling (ASL), and structural scans were also acquired, then analysed with separate processing streams in FEAT (FSL), CONN-toolbox (SPM12), ExploreASL (SPM12), and FreeSurfer. Data for regions of interest (ROI) based on previous findings were extracted and analyzed via general linear models (GLM) with multimodal ROIs as covariates.

Results: Bivariate correlations found mPFC-IE associations in BD (task fMRI r=.39, p=.035; cortical surface area morphometry r=.516, p=.005) but not HC (r=-.0.1, p=.971; r=.27, p=.273); RT also showed different patterns of association for BD (mPFC network rsFC r=.35, p=.071; ASL mPFC CBF r=-.44, p=.016) and HC (r=.60, p=.009; r=-.09, p=.716). In the GLM predicting IE within the BD group, the bivariate correlation for surface area was replicated (p=.035, \( n_2=-19\)), however, the task effect was reduced (\( n_2<.1\)) and rsFC became significant (p=.009, \( n_2=.27\)), suggesting a mediation relationship.

Conclusions: These preliminary results suggest that cognitive control in BD may be influenced by morphometry, CBF, and rsFC in addition to task neural response. Additional analyses, incorporating whole-brain and multivariate methods with greater sample size are ongoing.

Supported By: OMHF

Keywords: Bipolar Disorder, Cognitive control, Multimodal neuroimaging, Adolescents

533. Insights from EEG Microstate Analysis on the Pathophysiology of Depression and Mechanisms of Seizure Therapy

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Background: Converging neuroimaging evidence suggests that specific patterns of brain network dysfunction at rest may contribute to the core symptoms associated with Major Depressive Disorder (MDD). The efficacy of seizure therapy to treat MDD is hypothesized to be associated with the resetting of abnormal neural connectivity in MDD. In this study, a distinct methodology known as electroencephalogram (EEG) microstate analysis was used to evaluate functional brain network dynamics in patients with depression and after they received seizure therapy.

Methods: Resting-state 60-channel EEG data was obtained from 55 healthy subjects and 56 MDD patients. Of the 56 patients, 20 received Electroconvulsive Therapy (ECT) and 15 received Magnetic Seizure Therapy (MST). Resting-state EEG was recorded again at the completion of treatment. Three features were derived for each microstate class (A, B, C, D): frequency, duration and coverage time. The Hamilton Depression Scale was used to clinically assess patients prior to and following treatment.

Results: The relative frequency of microstate class D, previously linked with the frontoparietal network, was significantly higher in MDD patients but not in the healthy group. The frequency of this microstate class was also significantly reduced in MDD patients following ECT but not MST. Lastly, the frequency of this class at baseline was associated with change in symptoms such that a higher frequency of the class at baseline correlated with greater overall symptom improvement.

Conclusions: Provided that microstates can be recorded with portable and inexpensive EEG technology, these findings have important practical implications in translational research for patients with neuropsychiatric disorders.

Keywords: EEG Microstate Analysis, Major Depressive Disorder, Resting-state, Electroconvulsive Therapy, Magnetic Seizure Therapy

534. Having a Parent with Bipolar Disorder Promotes Learning Deficits even in Asymptomatic Bipolar Disorder Offspring

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Background: The prevalence of Bipolar Disorder (BD) among children and adolescents is around 1.8%.The impact of BD in the offspring is not restricted to mood symptoms, but also to neuropsychologic deficits, which can lead to poor functioning. In this study, we aim to evaluate the presence of learning problems among youth with BD, affected and unaffected offspring of parents with BD, and healthy controls.

Methods: This study included 114 youth with BD, 30 affected and 38 unaffected offspring of parents with BD, and 29 healthy controls. Participants underwent the Wechsler Abbreviated Scale of Intelligence (WASI), and Wide Range Achievement Test-Fourth Edition (WRAT-4).

Results: Comparisons of the study groups according to WRAT-4 scores for mathematics, and reading revealed that BD patients had significantly lower achievements than the other study groups (p values <.001, 0.012 respectively). The difference between groups showed a distribution as a progression model thus the best scores seen on healthy controls whereas the worst
scores seen on BD patients and unaffected and affected offspring lay between those. The same progression model is seen on processing speed and interference control parameters (p values <0.001, 0.015 respectively).

**Conclusions:** This was a pioneer study of learning deficits in youth with BD, increased risk for BD, and controls. Our results suggest that even unaffected offspring present significant learning difficulties, which may precede the development of symptoms and progression into full-blown mood disorder, and present as a new model to understand the development of BD. Our findings may add a very relevant component for preventive interventions.

**Keywords:** Bipolar Disorder, Offspring of parents with bipolar disorder, Neuropsychology, Neurocognition, Learning

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**535. Self-Reported Eating and Exercise Behaviors are Related to Mood and Cognition in Bipolar Disorder: An Ecological Momentary Assessment Study**

Tanya Nguyen, Sheena Dev, and Lisa Eyler

University of California, San Diego

**Background:** Diet and exercise habits have been linked to mood and cognition and may be risk factors for pathological brain aging. Few studies have utilized ecological momentary assessment in understanding health behaviors in bipolar disorder (BD). This study evaluated how eating and exercise relate to mood and cognition in BD.

**Methods:** Outpatients with BD (n=23) and healthy comparison subjects (HC; n=50) completed 3x-daily surveys on provided mobile devices over two weeks about eating and exercise behaviors as well as mood/affect. Subjects also completed measures of psychopathology and cognition at baseline. Mean levels and intra-individual variability (IIV) of momentary behavior ratings across time were calculated. We examined group differences in eating and exercise and their mood and cognitive correlates separately by group.

**Results:** Mean eating and exercise did not differ between groups, but BD patients demonstrated greater IIV in eating occasions compared to HC. Within BD, fewer eating occasions was associated with higher negative affect and depression ratings and lower mental wellness. Patients with poorer cognitive set-shifting and inhibitory control showed greater IIV in eating. Exercise was associated with greater participation in cognitively stimulating activities in both groups, as well as greater social engagement in BD.

**Conclusions:** Results of this preliminary investigation suggest that suboptimal eating behaviors are related to worse mood and cognitive functioning in BD. Additionally, those who exercise more generally engage in stimulating and social activities. Interventions aimed at promoting healthy diet and exercise behaviors may improve not only physical but also psychosocial and cognitive outcomes in BD.

**Supported By:** R01 MH083968

**Keywords:** Bipolar Disorder, ecological momentary assessment, diet, exercise, cognition

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**536. Cognitive Performance in Major Depressive Disorder in Generation Scotland: The Scottish Family Health Study (GS:SFHS)**

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University of Edinburgh

**Background:** Major Depressive Disorder (MDD) is a major cause of suffering and economic burden. Studies have shown that MDD patients perform significantly less well on some cognitive domains, which may be influenced by genetics.

**Methods:** Unrelated individuals (N = 7012) from the Generation Scotland cohort study were classified as either controls, single episode or recurrent MDD and assessed on several cognitive domains. Multiple linear regression was performed, controlling for sex, age, alcohol, smoking and socioeconomic status. A genome-wide association study (GWAS) and gene-by-MDD (GxMDD) scan were also performed to detect putative variants influencing cognitive differences between groups.

**Results:** The Mill Hill Vocabulary (MHV) score in both the control-MDD (β=0.744, p=2.47E-06) and control-recurrent MDD (β=0.965, p=4.62E-06) showed significantly increased performance in MDD in both study designs after Bonferroni adjustment. Significantly poorer performance on the Digit Symbol Substitution Test (DSST) was observed among recurrent MDD compared to single MDD (β=−2.752, p=0.002) and controls (β=−2.404, p=4.67E-04) after correction. The GWAS and GxMDD interaction analyses of these cognitive measures did not lead to significant associations after correction. rs911684 (p=3.99e-07) located in LOC100506999 showed the strongest association in the DSST GxMDD in the single-recurrent study design.

**Conclusions:** The MHV test, a well-validated measure of ‘verbal’ ability and an index of crystallised IQ, was significantly higher in MDD and recurrent MDD compared to controls. DSST, a ‘performance’ and more fluid IQ measure, was lower in recurrent MDD compared to controls and single episode MDD. No significant associations using GWAS or GxMDD scans were observed.

**Supported By:** Rosetrees Trust A655, University of Edinburgh Chancellors Fellowship, Scottish Government Health Department, Chief Scientist Office, Number CZD/16/6

**Keywords:** Major Depressive Disorder (MDD), cognition, Genetics, Genome-wide gene-environment interaction study, genome-wide association study

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**537. Attenuated Intrinsic Connectivity within Cognitive Control Network among Individuals with Remitted Depression is Associated with Cognitive Deficits and Negative Cognitive Styles**

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1University of Illinois at Chicago, 2University of Exeter

**Background:** Many individuals with major depressive disorder (MDD) experience cognitive dysfunction including impaired cognitive control and negative cognitive styles. Functional connectivity MRI studies of individuals with current MDD have...
documented altered resting-state connectivity within the default-mode network and across networks. However, no studies to date have evaluated the extent to which impaired connectivity within the cognitive control network (CCN) may underlie known cognitive phenotypes for MDD, particularly when individuals are in a remitted state.

**Methods:** In the present study, resting-state functional connectivity data were collected from 52 unmedicated young adults with remitted MDD (rMDD) and 45 demographically-matched healthy controls, using three bilateral seeds in the CCN (dorsolateral prefrontal cortex [dLIFC], inferior parietal lobule [IPL], and dorsal anterior cingulate cortex).

**Results:** Mean connectivity within the entire CCN was attenuated among individuals with rMDD, was stable and reliable over time, and was most pronounced from the right dLIFC and right IPL to the three bilateral CCN seeds. Attenuated connectivity in rMDD appeared to be specific to the CCN. In addition, connectivity between CCN seeds and regions of interest that differed in rMDD was associated with several known cognitive risk factors for depression, including ruminative brooding, pessimistic attributional style, negative automatic thoughts, inhibitory control, and inhibitory processing speed. Furthermore, attenuated CCN connectivity mediated relationships between rMDD status and cognitive risk factors.

**Conclusions:** Given that these cognitive markers are known predictors of relapse, these results suggest that connectivity within the CCN could represent a putative biomarker for trait phenotypes of depression risk.

**Supported By:** NIMH grant MH 091811 (SAL), and UIC Clinical and Translational Science Awards Program NCATS UL1TR000050 and 1S10RR028898.

**Keywords:** Major Depressive Disorder (MDD), Resting state functional connectivity, fMRI, Cognitive Control Network, cognitive style

### S218. **Blue Light Therapy following a Mild Traumatic Brain Injury Improves MPFC-Amygdala Functional Connectivity and Mood**

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**Background:** Mild traumatic brain injury (mTBI) has been associated with increases in anxiety subsequent to the injury. Dysfunction in functional connectivity of the medial frontal cortex (MPFC) and amygdala has been postulated to contribute to this incidence, perhaps via sleep disruption. We hypothesized that daily blue light therapy (BLT) would stabilize sleep for individuals recovering from a mTBI and this would contribute to increases in MPFC to amygdala functional connectivity and decreases in anxiety.

**Methods:** Twenty-six adults (14 female; M age: 21.6±3.9) who experienced a documented mTBI within the previous 18 months were enrolled. Subjects underwent six weeks of either BLT or a placebo amber light therapy (ALT) each morning for 30 minutes. Neurocognitive testing and a six-minute resting state functional magnetic resonance imaging scan occurred at baseline and following treatment. Regions of interest were placed in the MPFC and bilateral amygdala. Functional connectivity was analyzed utilizing the CONN toolbox, p<.05, FDR corrected.

**Results:** Significant increases in functional connectivity between the left amygdala and MPFC for individuals that received BLT were observed relative to ALT. This increase was associated with significant decreases in state anxiety and sleep onset latency between baseline and the conclusion of treatment.

**Conclusions:** BLT contributed to increased functional connectivity between the left amygdala and MPFC, which was associated with decreased anxiety symptoms. Findings suggest that BLT may facilitate entrainment the sleep wake cycle, which may facilitate cognitive and emotional recovery following a mTBI. Future work may examine the durability of this effect beyond the conclusion of treatment.

**Supported By:** DoD W81XWH-11-1-0056

**Keywords:** Concussion, mTBI, blue light, MPFC, Amygdala

### S276. **Brain Injury Improves MPFC-Amygdala Functional Connectivity in SZ Patients**

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1NCIRE/UCSF, 2University of California, San Francisco, 3NCIRE/University of California, San Francisco, 4Stanford University, 5Albert Einstein College of Medicine, 6Yale University School of Medicine

**Background:** Gamma oscillations coordinate neural activity and support neurocognitive function. Glutamatergic NMDA-receptors (NMDAR) modulate microcircuitry underlying gamma oscillations. Schizophrenia (SZ) is associated with abnormal EEG gamma band activity. Glutamatergic NMDAR hypofunction is a potential pathophysiological mechanism in SZ, mediating clinical and cognitive symptoms. Ketamine, an NMDAr antagonist, induces transient schizophrenia-like effect, including symptoms and changes in EEG, in both healthy humans and animals. The current study investigates the role of NMDAr hypofunction in abnormal gamma band activity in SZ by comparing the gamma band activity in healthy controls (HCs) following ketamine administration to that of SZ patients.

**Methods:** EEG auditory steady-state responses (ASSR) to 500ms click trains presented at 20, 30, and 40Hz, were recorded from 48 SZ patients and 51 HC subjects, and from 28 HC subjects administered intravenous saline or ketamine on separate test days in a randomized blinded cross-over design. Baseline gamma power (30-100Hz) preceding all click trains (~250 to -0ms) and 40Hz phase synchrony during the 40Hz click train (0-500ms in 100ms windows) were calculated from EEG single trials.

**Results:** SZ patients showed significant increases in baseline gamma power and decreases in 40Hz ASSR phase synchrony – particularly between 200 and 400ms. In contrast, ketamine significantly increased baseline gamma power, but did not impact 40 Hz ASSR phase synchrony in the same time windows where SZ effects were observed.

**Conclusions:** NMDAr hypofunction may mediate increased magnitude of intrinsic gamma activity in SZ patients but is less

### 539. **Ketamine, an NMDA-Receptor Antagonist, Mimics the Patterns of Intrinsically but Not Extrinsically Driven Gamma Oscillations**

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1NCIRE/UCSF, 2University of California, San Francisco, 3NCIRE/University of California, San Francisco, 4Stanford University, 5Albert Einstein College of Medicine, 6Yale University School of Medicine

**Background:** Gamma oscillations coordinate neural activity and support neurocognitive function. Glutamatergic NMDA-receptors (NMDAR) modulate microcircuitry underlying gamma oscillations. Schizophrenia (SZ) is associated with abnormal EEG gamma band activity. Glutamatergic NMDAR hypofunction is a potential pathophysiological mechanism in SZ, mediating clinical and cognitive symptoms. Ketamine, an NMDAr antagonist, induces transient schizophrenia-like effect, including symptoms and changes in EEG, in both healthy humans and animals. The current study investigates the role of NMDAr hypofunction in abnormal gamma band activity in SZ by comparing the gamma band activity in healthy controls (HCs) following ketamine administration to that of SZ patients.

**Methods:** EEG auditory steady-state responses (ASSR) to 500ms click trains presented at 20, 30, and 40Hz, were recorded from 48 SZ patients and 51 HC subjects, and from 28 HC subjects administered intravenous saline or ketamine on separate test days in a randomized blinded cross-over design. Baseline gamma power (30-100Hz) preceding all click trains (~250 to -0ms) and 40Hz phase synchrony during the 40Hz click train (0-500ms in 100ms windows) were calculated from EEG single trials.

**Results:** SZ patients showed significant increases in baseline gamma power and decreases in 40Hz ASSR phase synchrony – particularly between 200 and 400ms. In contrast, ketamine significantly increased baseline gamma power, but did not impact 40 Hz ASSR phase synchrony in the same time windows where SZ effects were observed.

**Conclusions:** NMDAr hypofunction may mediate increased magnitude of intrinsic gamma activity in SZ patients but is less
likely to mediate deficient synchronization of extrinsically-driven gamma oscillations.

**Supported By:** AstraZeneca, P50 AA012870/AA/NIAAA NIH, RO1 MH058262/MH/NIMH NIH, UL1 RR024139/RR/NCRR NIH

**Keywords:** Schizophrenia, Ketamine, NMDAR hypofunction, Gamma oscillation

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**540. Effects of N-methyl-D-aspartate Glutamate Receptor Disruption and Nicotinic Acetylcholine Enhancement on Mismatch Negativity**

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**Background:** N-methyl-D-aspartate glutamate receptor (NMDAR) hypofunction has been implicated in the pathophysiology of schizophrenia, including auditory processing abnormalities reflected by the mismatch negativity (MMN) event-related potential component. Evidence from animal models and healthy individuals suggesting cognitive benefits from nicotine administration, as well as the high rate of cigarette use in patients with schizophrenia, has stimulated interest in whether nicotine modulates NMDAR hypofunction in schizophrenia. Accordingly, we examined the interactive effects of ketamine, an NMDAR antagonist that produces transient schizophrenia-like behavioral and neurophysiological effects, and nicotine, a nicotinic acetylcholine receptor (nAChR) agonist, in healthy volunteers in order to determine whether nicotine prevents or attenuates MMN abnormalities.

**Methods:** Of 30 healthy volunteers enrolled, 27 participants completed four test days, during which they received ketamine and nicotine in a double-blind, counterbalanced design. Each test day involved two infusions, one either ketamine or placebo, and the other either nicotine or placebo. On each test day, MMN to duration double deviants) was assessed.

**Results:** Ketamine significantly decreased MMN amplitude for intensity-, pitch-, and double-deviant MMN. In contrast, nicotine significantly increased MMN amplitude, particularly for the double-deviant MMN. A significant ketamine x nicotine interaction indicated that while nicotine alone increased MMN, it failed to attenuate the decrease in MMN associated with ketamine.

**Conclusions:** These results demonstrate differential effects of nAChR and NMDAR systems on MMN, and further suggest that the detrimental effects of NMDAR blockade dominate when combined with the enhancing effects of nAChR augmentation.

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**Keywords:** Schizophrenia, NMDAR hypofunction, Ketamine, Nicotine,Mismatch Negativity

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**541. Deficits in and Compensation for Engagement of Social Cognition Areas in Schizophrenia during Naturalistic Viewing**

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**Background:** Social communication deficits are a major cause of psychosocial disability in schizophrenia patients (SzP). Studies of SzP have demonstrated potential differences in the multiple networks underlying social communication, but the interaction of these networks in naturalistic scenarios remains unclear. We recorded brain activity evoked by a cinematic movie in SzP vs. healthy controls (HC) to study these interactions.

**Methods:** 14 SzP and 14 HC underwent fMRI while watching 15 minutes of a movie, as well as task fMRI for localization of visual, face-processing, attention, and theory of mind areas, and resting state to measure connectivity of these areas. The timecourse for each voxel of BOLD activity evoked in each subject by the movie was correlated with the average timecourse of the HCs (inter-subject synchronization).

**Results:** Inter-subject synchronization maps were grossly similar in the two populations. Contrasting SzP and HC maps revealed reduced synchronization of visual and posterior STS face-emotion and theory of mind areas. Resting state connectivity of these areas was also reduced in SzP, resulting in a disconnection of visual and theory of mind areas. However, SzP demonstrated increased synchronization of dorsal attention areas as compared to HC, indicating that use of these areas was increased in SzP.

**Conclusions:** This study demonstrates the utility of naturalistic viewing paradigms to simultaneously evaluate the functioning of multiple networks in Sz. We find deficits in the engagement of visual and face-emotion processing areas that mirror the deficits in connectivity. Increased engagement of attention networks may represent compensation for the visual/face-emotion processing deficits.

**Supported By:** NIMH, Leon Levy Foundation, American Psychiatric Foundation

**Keywords:** BOLD fMRI, Resting state functional connectivity, Social Cognition, emotional face processing, attention

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**542. Cannabis Use and Neurocognitive Functioning in the Psychosis Spectrum**

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**Background:** Schizophrenia is characterized by significant neurocognitive deficits. Meta-analyses suggest that individuals...
with schizophrenia who use cannabis show better cognitive functioning compared to those who are non-users. Here, we extend prior research to examine whether associations between frequency of cannabis use and cognitive functioning extend beyond schizophrenia and frank psychotic disorders to individuals with psychosis spectrum symptoms.

**Methods:** The sample included 3,620 youths aged 14-21 drawn from the Philadelphia Neurodevelopmental Cohort, including 804 who were classified as psychosis spectrum (PS) (including 97 Frequent Cannabis Users [FCU] and 707 Non-Users [NU]) and 2,816 classified as non-PS (including 134 FCU and 2,682 NU). Cognitive functioning was assessed using the Penn Computerized Neurocognitive Battery (CNB), which examines a broad range of cognitive functions. Mixed-effects models examined main effects and interactions of cannabis use and PS status for predicting cognitive functioning.

**Results:** PS showed worse cognitive performance across domains compared to non-PS (p<.0001). There was a significant interaction between cannabis use and PS status in memory (p=.01) and complex cognition (p=.008). Follow-up analyses showed that FCU had better cognitive performance than NU across domains within the PS group (p<.01), although cannabis groups performed similarly within the non-PS group (p=.10).

**Conclusions:** Findings indicated that PS youths who frequently used cannabis had less impaired cognitive functioning than PS youths who did not use cannabis in episodic memory and complex cognitive processing (e.g., verbal and non-verbal reasoning). Differences in cognitive performance by cannabis use may be informative for understanding risk for and resilience to brain-behavior dysfunction in psychosis.

**Supported By:** NIH MH089983

**Keywords:** Cannabis, Neuropsychology, psychosis phenotype, Psychosis-Proneness, Memory

**543. Dysregulated Affective Neural Processing in Schizophrenia Patients and Controls following Psychosocial Stress Exposure**

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**Background:** Emotion regulation (ER) is fundamental to the development, maintenance and treatment of neuropsychiatric disorders, including schizophrenia (SCZ). Effective ER relies on communication among distributed fronto-limbic brain regions, supported by synchronized neural oscillations in distinct frequency bands, including theta and beta. While evidence suggests that stress interferes with the successful implementation of ER strategies by disrupting frontal neural activity, its influence on oscillatory activity in SCZ patients remains unknown. This study investigated the effect of stress on EEG measures of oscillatory activity during emotional framing of aversive stimuli.

**Methods:** EEG and ECG were recorded from SCZ (n=21) and healthy controls (CON; n=21) while they performed an emotional oddball framing task before and after a psychosocial stressor (TSST). The task prompted participants to categorize aversive stimuli as positive or negative using simple framing cues.

**Results:** Patients demonstrated reduced frontal theta (4-8Hz) relative to controls (p<.05), and aberrant affective regulation, with increased parietal beta (13-30Hz) (p<.05). Despite enhanced physiological measures of stress (RSA), patients exhibited relatively stable EEG correlates of affective processing following stress. Conversely, stress exposure disrupted affective processing in CON, with enhanced frontal theta and parietal beta activity after stress (p<.05).

**Conclusions:** Results suggest that patients exhibit aberrant neural correlates of affective processing, yet deficits are not further exasperated by stress. Nevertheless, stress disrupted affective processing in CON, causing deficiencies in frontal theta and heightened emotional beta activity. Dysregulated affective neural processing observed in SCZ, and CON after stress, may impact the ability to effectively employ cognitive therapies reliant on ER during stressful situations.

**Supported By:** NARSAD

**Keywords:** Emotion Regulation, Psychosocial Stress, EEG, Schizophrenia

**544. Delusional Ideation in Psychosis Correlates with Decreased Left Prefrontal NAA**

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**Background:** Delusions remain a disabling and often treatment-refractory symptom of psychiatric illness. Our increasing understanding of the neurobiology of learning and memory makes the pathophysiology of delusions a more tractable problem. Furthermore, some psychotic symptoms may exist on a spectrum from health to illness. While decreases in gray matter and disturbances in metabolites in frontal cortex are known to be associated with psychosis, this association has not been shown specifically with delusions in psychosis.

**Methods:** Ten healthy volunteers and eleven medicated or unmedicated psychotic patients were given Peters Delusional Inventories (PDI), and also underwent magnetic resonance spectroscopy scans at 3T using PRESS with 80 millisecond echo times to provide glutamate as a measure of neurotransmission and NAA as a marker of neurons. Peters Delusional Inventories for volunteers and patients were analyzed by two-tailed t test. Pearson's correlation was calculated for glutamate normalized to creatine against total PDI scores.

**Results:** PDI scores for volunteers and patients completing the inventory were significantly different with p<.01. In patients, worse delusional ideation was significantly associated with less left middle frontal NAA (p<.05); most groups showed trend level inverse correlations as well with glutamate and NAA.

**Conclusions:** This shows that delusional ideation is associated with a decrease in NAA and by extension neuronal density in left prefrontal cortex. Most interestingly thusfar the correlation holds only for patients. This provides clues as to the underlying anatomy of delusional ideation and can focus further investigation.

**Supported By:** NIMH R01 MH105411

**Keywords:** delusions, MRS, Schizophrenia, NAA, Glutamate
545. Effects of tDCS on Cognitive Control and Cortical Network Oscillations in Schizophrenia

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Background: Deficits in proactive cognitive control are consistently observed in patients with schizophrenia (Sz), are correlated with behavioral disorganization and functioning, and associated with decreased activity in the dorsolateral prefrontal cortex (DLPFC). Treatment options for impaired cognition in schizophrenia have been limited to date. We used tDCS of left DLPFC in an effort to restore proactive control performance in Sz and used EEG as a readout of engagement of the cognitive control network in the brain.

Methods: In an ongoing double blind paradigm, 10 patients with Sz underwent 20 min of active and sham left DLPFC anodal tDCS during the N-Back task. Stimulation was followed by EEG recordings during the Dot Pattern Expectancy Task, a proactive control task known to engage the prefrontal cortex.

Results: tDCS led to partial restoration of goal maintenance, shifting the relative number of errors on AY and BX trials. Time frequency analysis of induced EEG showed modulation of oscillatory activity in bilateral DLPFC and related elements of the cognitive control circuitry. Data collection is ongoing and analyses of an expanded sample (n=20) will be presented.

Conclusions: tDCS over the DLPFC may partially restore deficits in proactive control in patients with Sz. tDCS has therapeutic potential for restoring disruptions in synchronous oscillations that may underlie cognitive dysfunction.

Supported By: Office of Naval Research, Mental Health Pilot Award

Keywords: cognitive control, Schizophrenia, tDCS, EEG

546. A Comparative Study of Accuracy of Self-Assessment in Bipolar and Schizophrenia Patients Focusing on Employment and Living Status

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Background: While self-assessments are frequently used as outcome measures in the evaluation of interventions for severe mental illnesses, there is considerable evidence that these reports can be inaccurate. The purpose of this study is to understand the relationship between self-assessment of disability relative to objective functional achievement as defined by everyday milestones in patients with bipolar (BP) and schizophrenia spectrum disorders (SCZ).

Methods: The sample is from the Suffolk County Mental Health Project and participants were entered after their first psychotic episode; 146 with schizophrenia spectrum disorders and 87 bipolar disorder. We compared self-assessments of the (WHODAS) with interviewer-ascertained outcome data: independence in residence and gainful employment.

Results: Compared to schizophrenic patients, patients with bipolar disorder evaluated themselves as more capable and they were more likely to have achieved current milestones (Work: SCZ 25%; BP 53%; Independence: SCZ 46%; BP 86%). Employment in the bipolar group predicts a more accurate self-assessment of functionality in comparison of their unemployed counterparts (7 versus 2 ill days, p<.05). This was also true in schizophrenia group when reporting global disability. Bipolar patients who lived independently reported less disability overall (p<.05).

Conclusions: Patients with bipolar disorder and schizophrenia manifested similar patterns of mis-estimation in their functioning, with minimal differences throughout both groups. Having employment in bipolar group leads to more accurate self-assessment of functioning in comparison of their unemployed counterparts. This was also true in schizophrenia group when reporting global disability. But overall, relative to objective measures both groups have a similar pattern of mis-estimating their ability to function.

Keywords: Bipolar Disorder, functional outcome, Schizophrenia

547. Deficits in Attentional Modulation of Sensory ERPS in First Episode Schizophrenia

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Background: The N1 auditory evoked potential is reduced in long-term schizophrenia (Sz) and in the first episode schizophrenia spectrum (FE). N1 is increased by attention to tones, and this effect is impaired in Sz. It is not known whether FE can modulate N1 sensory signals by attention.

Methods: Thirteen FE and 11 matched healthy controls (HC) heard 340 tones (1 kHz, 50 ms duration, 5 ms rise/fall, SOA=1050-1550 ms) while watching a silent nature video. In one block, participants were told to ignore tones. In another, participants pressed a button to every 7th tone. Blocks were counter-balanced. Mean N1 amplitudes (100-110 ms after stimulus onset) were compared between ignore/attend conditions and groups.

Results: Of primary importance was a significant interaction between effects of group and attention (p=.029). HC showed larger N1 in the attend condition compared to FE (p=.03), but there was no group difference in the ignore condition (p>.1).

Conclusions: FE did not appear to enhance the auditory N1 with attention. This may reflect a long-range functional disconnection between cognitive control cortical areas and sensory cortex early in disease course. Clinically, the lack of N1 modulation may serve as a sensitive biomarker for the detection of the schizophrenia prodrome among clinical high-risk individuals.

Supported By: NARSAD, NIH R01 MH108568

Keywords: N100, Schizophrenia, First-Episode Psychosis (FEP), Attention
548. Neural Mechanisms of Impaired Learning from Errors in Dependent Smokers

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**Background:** Punishing errors facilitates adaptation in healthy people, while aberrant reward and punishment sensitivity in drug dependence may change this effect. Recent research has identified the insula cortex to predict learning from highly aversive outcomes. As most legal systems use the concept of punishing errors, it is vital to explore how negative feedback influences adaptive behaviour in drug dependency.

**Methods:** Using an associative learning task, we investigated differences in error correction rates for number-location pairs in dependent smokers compared to controls. We administered two versions of the task: one assessed the effect of varying monetary values in an MRI scanner, the other one assessed the presence of reward as opposed to mere avoidance of punishment for correct performance.

**Results:** Two group (Smoker, Control) by two magnitude condition (5c, 50c) repeated measures ANOVAs examined within-subject factors feedback type and magnitude of feedback on the between subject factor of smoking group: While smokers recalled locations that were rewarded with a higher value (50cents) 11% more than lower rewarded locations (5cents), but did not correct higher punished locations more, controls exhibited the opposite pattern. We found lower activation of the insula in smokers during feedback presentation of highly punished locations.

**Conclusions:** The results suggest that smokers have poorer learning from errors when the feedback is negative. High rewards reinforce smokers' behaviour stronger than low rewards, whereas controls make no distinction. These findings should be incorporated into the design of anti-smoking therapies, where the appeal to quit smoking is incentivised through reward rather than punishment.

**Supported By:** Australian NIMHRC

**Keywords:** Error Processing, Cognitive Neuroscience, Reward Learning, drug addiction

549. DNA Methylation Biomarkers and Treatment Effects of a Corticotropic Releasing Hormone Type 1 Receptor Antagonist in a Biologically-Defined Subset of PTSD-Patients

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**Background:** We evaluated the efficacy of a CRHR1-antagonist (GSK561679) in female PTSD patients. While the drug was not superior to placebo overall, it was associated with a significantly stronger symptom reduction in a subset of patients with probable CRHR1 hyperactivity, i.e., patients with early trauma (ET) and carriers of the GG-genotype of the CRHR1-SNP rs110402. Here we aimed to test whether blood-based epigenetic biomarkers that had previously been shown to predict PTSD symptom change after psychotherapy would also be associated with treatment outcome with the CRHR1 antagonist in the relevant subgroup.

**Methods:** Genome-wide genotypes (Illumina-OmniExpress-array) and DNA methylation (Illumina-450K-methylation-array) in blood and psychological assessments in a cohort of PTSD-diagnosed women (18-65 years) treated with CRHR1-antagonist (N=44) or placebo (N=45) over six weeks.

**Results:** We specifically tested CpGs in the promotor region of NR3C1 and FKBP5 previously described to associate with treatment outcome after psychotherapy. Of these, four were present on the Illumina-450K-array for NR3C1 and three for FKBP5. NR3C1 cg04111177 baseline methylation significantly interacted with early trauma (ET) to predict change in the PTSD-symptom-scale (PSS) following treatment with CRHR1-antagonist (n=39;p=0.016), but not with placebo. Interestingly this effect was most pronounced for the PSS-subscapes re-experiencing (p=0.014) and avoidance (p=0.003). In a post hoc analysis in CRHR1-antagonist treated patients with ET, we observed that the effect of methylation on PSS-change was most prominent in GG-allele carriers. No significant effects were observed for FKBP5.

**Conclusions:** Our results support that epigenetic biomarkers associate with PTSD-treatment outcome and validate biologically relevant subgroups that may preferentially respond to novel treatments.

**Supported By:** NIMH grant: U19 MH069056; VA grant: VA CSRD Project ID 09S-NIMH-002; clinicaltrials.gov number: NCT01018992

**Keywords:** PTSD - Posttraumatic Stress Disorder, CRHR1 antagonist, NR3C1, FKBP5, Epigenetic biomarkers

550. Delineating Transcriptomic Profiles in PTSD: An RNAseq Investigation

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**Background:** Post-traumatic stress disorder (PTSD) is a debilitating neuropsychiatric disorder underpinned by complex, multi-factorial interactions. To date, most genetic studies have only focused on specific candidate genes involved in PTSD and therefore, lack a holistic view that can be gained by a whole-transcriptome (RNAseq) approach. We aimed to utilise RNAseq in order to investigate molecular mechanisms and possible biomarkers in South African PTSD patients.

**Methods:** This case-control study design South African Coloured female individuals diagnosed with PTSD (n=19) were compared to trauma-exposed control (n=29) individuals. RNA was extracted from whole blood and sent for RNA-Seq using the Illumina HiSeq4000 platform at a sequencing depth of 50 million paired-end reads. Bioinformatics analyses were then performed, followed by downstream co-expression analysis to investigate co-regulated differentially expressed gene sets between groups.
Results: A total of 556 differentially expressed genes were identified, of which 196 (22 upregulated and 174 downregulated) genes were determined to be biologically relevant based on an ontology-driven prioritisation approach. Co-expression analysis revealed a network of 4 highly co-expressed upregulated genes and a large co-expression network consisting of 36 downregulated genes. The 4 co-expressed upregulated genes (RPL6, RPS6, RPS3A and EEF1B2) and 6 highly connected co-expressed downregulated genes (DHX9, BCLAF1, THRAP3, EIF4G1, HSPA4 and MCL1) were identified as potentially relevant links contributing to the pathology of PTSD.

Conclusions: This hypothesis-generating study identifies genes possibly involved in the molecular underpinnings of PTSD in a cohort of South African mixed ancestry females, and forms the basis of larger replication studies, which are currently underway.

Supported By: South African Medical Research Council
Keywords: PTSD - Posttraumatic Stress Disorder, transcriptome

551. Maternal History of Early Adversity and Offspring Temperament: Investigating Rearing Environmental and Genetic Contributions
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Background: We examined the mediating role of maternal symptoms of depression in the relation between maternal history of early adversity and child negative emotionality/behavioural dysregulation (NE/BD) in 169 mother-child dyads. We hypothesized that offspring would be differentially affected as a function of their polygenic risk score (PRS) for major depressive disorder (MDD).

Methods: Maternal childhood experiences were assessed with an integrated measure derived from the Childhood Trauma Questionnaire and the Parental Bonding Index. Maternal symptoms of depression were rated with the Edinburgh Postnatal Depression Scale. Offspring genotype was assessed using the Illumina PsychChip Array which genotypes more than 588,000 markers. We computed a PRS for MDD, using the Psychiatric Genomics Consortium as a discovery sample. A measure of NE/BD was derived from the Early Childhood Behaviour Questionnaire.

Results: Mediation models suggested an indirect effect of maternal adversity on child NE/BD through maternal symptoms of depression (β = .069; 95% CI = 0.026 to 0.144). This mediation varied as a function of child PRS (Index = .0521; 95% CI = -.154 to .002): children with a low to medium genetic risk for MDD showed a stronger association between maternal symptoms of depression and child NE/BD. There was also a main effect for child MDD PRS on NE/BD, with children having a higher genetic risk predicting higher scores of NE/BD (β = .332; 95% CI = .092 to .572).

Conclusions: Results suggest the intergenerational risk transmission of maternal history of adversity and shed light onto offspring genetic makeup in shaping their response to the environment.

Supported By: Canadian Institutes for Health Research; Faculty of Medicine of McGill University; Ludmer Foundation; Sackler Foundation
Keywords: Maternal Adversity, Maternal Depression, Polygenic Risk Score, Child Temperament

552. Methylation of Hypothalamic-Pituitary-Adrenal Axis Related Genes in Men with Hypersexual Disorder
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Background: Hypersexual Disorder (HD) defined as non-paraphilic sexual desire disorder with components of compulsivity, impulsivity and behavioral addiction was proposed as a diagnosis in the DSM 5. In this study, comprising 67 HD male patients and 39 male healthy volunteers, we aimed to identify HPA-axis coupled CpG-sites, in which modifications of the epigenetic profile are associated with HD.

Methods: The genome-wide methylation pattern was measured in whole blood using the Illumina Infinium Methylation EPIC BeadChip, measuring the methylation state of over 850 K CpG sites. The global DNA methylation pattern was pre-processed according to standard protocols and adjusted for white blood cell type heterogeneity. We included CpG sites located within 2000 bp of the transcriptional start site of the following HPA-axis coupled genes: CRH, CRHBP, CRHR1, CRHR2, FKBP5 and NR3C1. We performed multiple linear regression models of methylation M-values to a categorical variable of HD, adjusting for depression, DST non-suppression status, Childhood Trauma Questionnaire total score and plasma levels of TNF-alpha and IL-6.

Results: Of 76 tested individual CpG sites, four were nominally significant (p<0.05), associated with the genes CRH, CRHR2 and NR3C1. Cg23409074 – located 48 bp upstream of the TSS of the CRH gene – was significantly hypomethylated in HD patients after corrections for multiple testing using the FDR-method. Methylation levels of cg23409074 were positively correlated with gene expression of the CRH gene in an independent cohort of 11 healthy men.

Conclusions: CRH is an important integrator of neuroendocrine stress responses in the brain, with a key role in the addiction processes.

Supported By: Swedish Research Council and the Swedish Brain Research Foundation (Helgi Schiöth) and through a regional agreement between Umeå University and Västerbotten County Council (ALF) and by grants provided by the Stockholm County Council (ALF and PPG projects) (Jussi Jokinen).
Keywords: HPA axis, Epigenetic, Addiction, CRH, Childhood Trauma

553. Psychiatric and Cognitive Phenotyping of Youth with McCune-Albright Syndrome: Clinical Findings in Support of a Neurobiological Mechanism
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Supported By: Swedish Research Council and the Swedish Brain Research Foundation (Helgi Schiöth) and through a regional agreement between Umeå University and Västerbotten County Council (ALF) and by grants provided by the Stockholm County Council (ALF and PPG projects) (Jussi Jokinen).
Keywords: HPA axis, Epigenetic, Addiction, CRH, Childhood Trauma

Friday Abstracts
Background: McCune-Albright syndrome (MAS) is a rare genetic condition arising from a somatic activating mutation of GNAS, which leads to overproduction of cAMP. The mutation can involve any or all embryological layers leading to a wide variety of clinical manifestations such as fibrous dysplasia and café-au-lait spots (often lateralized), as well as endocrinopathies. This study describes psychiatric and neuropsychological findings among youth with MAS, which may be associated with neurobiological mechanisms underlying MAS pathophysiology.

Methods: This is a cross-sectional study of patients with MAS ages 8 to 25 who are enrolled in a natural history study. Eighteen underwent a structured psychiatric interview; a subset (N=11) underwent neuropsychological evaluation.

Results: Mean age of the subjects was 15.7 years and 55.6% were female. Eleven of eighteen subjects (61.1%) met criteria for a current psychiatric disorder: anxiety (38.9%), mood (22.2%), and psychotic disorders (16.7%). Thirteen of eighteen (72.2%) met criteria for a lifetime psychiatric disorder: anxiety (55.6%), mood (33.3%), and psychotic disorders (16.7%). While the mean full-scale IQ score (104.9; SD=15.1) was within the average range, the magnitude of discrepancy between verbal and nonverbal intelligence was markedly elevated: 38.7% higher than in the general population.

Conclusions: The rate of psychopathology in this cohort of youth with MAS is remarkably high compared with the general population. In addition, neuropsychological findings suggest possible lateralization of brain involvement. Our findings lend support to the further study of neurobiological mechanisms in specific brain regions/circuits expressing the GNAS mutation that may underlie the development of psychiatric and cognitive abnormalities.

Supported By: NIMH Intramural Research Program, Office of the Clinical Director

Keywords: Genetics, Rare Disorders, Neurobiology, Phenotyping, Youth

554. Application of Growth Mixture Modeling in Antidepressant Treatment Response Studies

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Background: There is heterogeneity in the therapeutic response to antidepressant among major depressive disorder (MDD) patients.

Methods: We investigated studies without and with placebo arm in their response trajectories by applying growth mixture modeling (GMM) to the clinical datasets from the STAR*D study and a Janssen clinical trial. The best growth mixture model was compared to a latent class model based on baseline DSM-IV depression symptom and selected IDS items alone. Both models were characterized by their treatment response outcome and other clinical characteristics. Furthermore, genetic predictors were used to predict the class membership as compared to shared controls.

Results: In each of the active treatment arms the best growth mixture model is a three class mixture model representing a non-response group (class 1), a responder group with moderate baseline severity (class 2), and a responder group with severe baseline symptom severity (class 3). Class 1 group had high suicidality (68% vs. 42%) and more comorbid anxiety disorder especially PTSD compared to class 2. The GMM identified classes of different characteristics than the classes identified in the latent class analysis (LCA). The three response trajectories identified by GMM were also observed in an independent Janssen clinical study although the proportion of three classes differed. Despite the small sample size from STAR*D genetic subsamples, the preliminary genetic association with the GMM and LCA posterior class membership vs. shared healthy controls identified potential loci of interest.

Conclusions: The growth mixture model from two independent clinical datasets identified classes of similar response trajectory.

Keywords: Major Depression

555. Gene Expression Differences Associated with Major Psychiatric Disorders in the Human Prefrontal Cortex and Hippocampus

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Background: Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ) are serious psychiatric illnesses with largely uncharacterized pathophysiology. Gene expression characterization in tissue from disease-relevant regions like dorsolateral prefrontal cortex (DLPFC) and hippocampus can improve our understanding of each disease.

Methods: We use RNA-seq to perform four experiments looking at differential gene expression in human DLPFC: MDD patients (n=146) and controls (n=224), BD patients (n=69) and controls (n=224), and two experiments in SCZ patients (n=181; n=163) and controls (n=224; n=236). In a fifth, we examined SCZ patients (n=133) and controls (n=248) in hippocampus. Experiments were adjusted for age, sex, postmortem interval, ancestry, RIN, mitochondrial mapping rate, and latent variation with surrogate variable analysis.

Results: We found significant evidence (false discovery rate of q<0.05) for 133 differentially expressed genes (DEG) MDD patients, 87 DEG in BD patients, 128 DEG in SCZ patients in the hippocampus, 47 DEG in SCZ patients in the first experiment in the DLPFC and 13 DEG in the second. Several genes were significant across disorders: LIF is upregulated in MDD, BD and SCZ and IL1RL1 is upregulated in BD and SCZ.

Conclusions: LIF, a member of the IL6 cytokine family, interacts with gp130 as well as stimulates ACTH secretion and is differentially expressed (DE) in MDD, BD, and SCZ, potentially a generalized marker of psychiatric illness. IL1RL1 encodes a receptor for IL33 and is DE in BD and SCZ.
suggested a role in disorders with psychotic features. Our findings provide novel insights into the pathophysiology of MDD, BD, and SCZ.

Keywords: RNA-seq, Major Depressive Disorder (MDD), Schizophrenia, Bipolar Disorder, cross-disorder

556. Adiponectin Gene Polymorphism and Seasonality in the Old Order Amish

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Background: Seasonal changes in mammals are considered adaptive physiological capabilities to use temporal cues (e.g. photoperiod) to anticipate rather than purely react to seasonal harsh thermoregulatory demands combined with scarce food availability. We have recently reported that levels of adiponectin – an adipocytokine with anti-inflammatory activity, levels of which are found to be decreased in obesity, diabetes, and hypertension as well as in depression – are lower in Amish individuals with seasonal affective disorder (SAD) than in those without SAD. As a SNP of the adiponectin gene has been previously linked with adiponectin levels, we examined the relationship between the adiponectin SNP rs2241766 and mood seasonality. We also analyzed associations of seasonality with SNPs previously associated with SAD, obesity, BMI, and metabolic syndrome.

Methods: We studied 863 participants (418 men and 445 women, age = 56.0 ± 15.3 years) from the Amish Complex Genetic Disease Research Program with both global seasonality scores (GSS), calculated from the Seasonality Pattern Assessment Questionnaires) and 1,000 genome imputation genotype data. TA mixed models were employed to test GSS vs. “metabolic” SNPs associations.

Results: Following adjustment for age, sex, and BMI, rs2241766 was associated with GSS (β = 0.77, SE = 0.30, p = 0.01). The association of neither rs2241766 nor any other candidate SNP with GSS withstood adjustment for multiple comparisons.

Conclusions: Our findings did not support the hypothesized associations between "metabolic" SNPs and GSS. Longitudinal and interventional approaches will be further used to investigate the adiponectin-seasonality link. In the long run this may lead to flattening fall/winter increases in food craving, intake, and BMI.

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Keywords: adiponectin, gene polymorphisms, seasonality, seasonal affective disorder, Amish

557. Pharmacogenetic Association of Lithium Treatment Response with Bcl2 Polymorphism in Bipolar Disorder

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Background: Lithium is first line drug for treatment of Bipolar Disorder (BD), however it mechanism is still not known. Bcl2 is a anti apoptotic protein whose gene maps to 18q21.3. Linkage studies have suggested that 18q21-22 locus harbours risk genes for BD(McMahon et al., 2001) Recent studies showed suggestive role of Bcl2 in pathophysiology of BD(Chen et al. 2015; Séeiro-de-Souza et al. 2013). The current study is to see association of Bcl2 rs956572 polymorphism with lithium treatment response in BD

Methods: BD subjects (N = 226) using DSMIV criteria were recruited from the outpatient service of NIMHANS. Treatment response was assessed using “Retrospective criteria of long term treatment response in research subjects with bipolar disorder” for whom NIMH life charts were available (n = 187). DNA was isolated from peripheral blood and genotyping of Bcl2 rs956572 was carried out using RFLP (n = 163).

Results: Mean age at onset for BD (N = 226) was 21.1 ± 6.2 years. Subjects treated with lithium (n = 187) were categorised as excellent responders (53.7%, score ≥ 7), partial responders (24.6%, score 4–6) and non-responders (17.6%, score ≤3). No statistical difference was noted among the clinical variables between different treatment response groups. The genotype frequencies in the study group followed the Hardy Weinberg equilibrium. There was no association of this SNP with clinical parameters like age of onset and response to lithium treatment (χ²= 3.81 and p = 0.14)

Conclusions: No association is found with Bcl2 polymorphism and lithium response

Keywords: Bipolar Disorder, bcl2, lithium response

558. Association of CRHR1 TAT Haplotype with Cognitive Features of Major Depressive Disorder

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Background: Corticotropin-releasing-hormone (CRH) signaling through CRH receptor 1 has been shown to contribute to morphological changes in the hippocampus and alterations in learning and memory function. A haplotype of alleles T-A-T in a set of common polymorphisms in the gene encoding for CRH receptor 1 (CRHR1) has been associated with depression vulnerability, elevated cortisol, and alterations in cognitive functioning. The present study investigated the relationship between the TAT haplotype and specific symptoms of depression, self-reported ruminative behaviors, and neuro-psychological performance on a learning and memory task.
Methods: Participants were adults with major depression with and without psychotic features (N=406). Associations were examined between TAT haplotype and endorsement of specific depression symptoms from diagnostic interviews, scores on the Ruminative Response Scale (RRS), and verbal memory performance on the California Verbal Learning Test-II (CVLT-II). Analyses included depression subtype and age as covariates.

Results: Across all depressed individuals, carriers of more copies of the TAT haplotype reported greater endorsement of depressed mood (β(11)=6.64, p=0.010) and problems concentrating/making decisions (β(11)=6.85, p=0.009). In subsamples of depressed individuals, TAT homozygotes were found to have higher brooding rumination scores on the RRS (F(2,181)=4.20, p=0.017) and increasing numbers of TAT copies were associated with poorer CVLT-II performance (F(1,50)=7.76, p=0.008), accounting for 10.8% of the variance.

Conclusions: These data demonstrate that the TAT haplotype is associated with a cognitive style that is expressed as difficulty with decision-making, higher rumination, and poorer learning and memory, which implicates CRH signaling in depression-related cognitive dysfunction.

Supported By: Pritzker Foundation, NIH MH50604 and MH19938 to Alan Schatzberg, NIH MH74849 and MH101495 Pritzker Foundation, NIH MH50604 and depression-related cognitive dysfunction.

Keywords: Major Depression, TAT haplotype, CRHR1, Rumination, Cognition

559. Genome-Wide DNA Methylation Analysis of High-Dose Synthetic Glucocorticoid Administration within Buccal Samples of Oral Surgery Patients

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Background: Glucocorticoids play a major role in regulating the stress response, and an imbalance of glucocorticoids has been implicated in stress-related disorders. Within mouse models, candidate genes have been shown to be differentially methylated in response to glucocorticoid treatment. However, within humans the extent to which glucocorticoids affect DNA methylation (DNAm) across the genome is unknown.

Methods: Buccal samples were collected before and after glucocorticoid treatment in the context of oral surgery. This included 22 minor tooth extraction surgery patients who received 10 mg of dexamethasone, and six major jaw surgery patients who received 750-1,000 mg of methylprednisolone. Genome-wide DNAm was assessed with the Infinium HumanMethylationEPIC array. Data were processed and analyzed with the R package RnBeads. Statistical significance was determined using the paired student’s t-test. The genome-wide significance threshold for this experiment is p<5.15 x 10-8.

Results: Within the minor surgery samples, the most significantly different CpG in the before vs. after treatment comparison was within the long intergenic non-coding RNA LINC00478 (average DNAm: pre-steroid 90%, post-steroid 80%; p=1.79 x 10-7). Average differences of over 10% were seen for 1,954 CpGs. Within major surgery subjects, the top differentially methylated CpG was within heat shock transcription factor 2 (HSF2; average DNAm: pre-steroid 79%, post-steroid 91%; p=3.21 x 10-5). Average differences greater than 20% were seen in 407 CpGs.

Conclusions: High-dose synthetic glucocorticoid administration in the setting of oral surgery is nominally associated with DNAm changes within buccal samples. These findings provide initial evidence for an influence of glucocorticoids on DNAm within humans.

Keywords: Epigenetics, Glucocorticoids, DNA methylation, Stress, EWAS

560. CRH R1 Genotype and Sleep Electroencephalogram in Healthy Subjects

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Background: Corticotropin releasing hormone (CRH) plays key roles in modulation of behavioral and neuroendocrine responses to stress and in sleep regulation. CRH overactivity contributes to the pathophysiology of mood disorders including sleep-EEG changes in patients with depression as reduced slow-wave sleep (SWS) and disinhibition of rapid-eye-movement (REM) sleep. Polymorphisms of the CRH receptor CRH R1 gene appear to be associated with the risk to develop mood disorders. These include the single nucleotide polymorphisms (SNP) rs110402 and rs7209436. We investigated associations between these SNPs and sleep EEG in healthy male volunteers.

Methods: Sleep EEG was recorded in 91 young healthy male volunteers between 23:00 and 07:00. Psychiatric disorders were excluded in their own and family history. Conventional sleep-EEG analysis was performed according to standard criteria. Homozygous TT and CC and heterozygous CT carriers of both SNPs were compared. p-values were corrected for multiple testing through resampling according to Westfall and Young.

Results: The relative time spent in SWS was highest in TT carriers (n=28), mean ±S.E.M. 24.0 ± 2.0 %, lower in CT(n=45), 21.3 ± 1.0 % and lowest in CC (n=18), 17.5 ± 5.1 min;p=0.003; REM time was lowest in TT and highest in CC (ns). These findings resemble the decrease of SWS in depressed patients. Interestingly no significant association between REM variables and this genotype was found. Our findings are in line with the view that CRH contributes to impaired sleep in depression.

Keywords: CRH-R1, Sleep, rs110402, rs7209436, Depression
561. Discovery, Replication, and Application of an Epigenetic Biomarker Model to the Prediction of Postpartum Depression and Neuroimaging Endophenotypes

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Background: We hypothesize that postpartum depression (PPD) risk may arise from an altered sensitivity of the epigenetic reprogramming machinery to hormonal change. We previously identified estradiol responsive DNA methylation changes in the mouse hippocampus that correlate to human blood epigenetic differences in women at risk to PPD. We algorithmically identified two biomarker loci at TTC9B and HP1BP3 capable of PPD prediction with > 80% accuracy. The objective was to validate model predictive accuracy and expand our understanding of the biological consequences of these changes using hormone analysis and fMRI.

Methods: DNA methylation of TTC9B, HP1BP3, and a proxy of blood cell proportions were assessed with sodium bisulfite pyrosequencing in women subjected to gonadotropin releasing hormone receptor agonist (GnRHa), a prospective PPD cohort without mood disorder, and a PPD cohort of women with previous mood disorder undergoing fMRI. Random forest models were applied to predict depressive symptoms in each cohort.

Results: The model predicted depression symptoms in the GnRHa dataset upon estrogen withdrawal with 80% accuracy. In the general population, Edinburgh Postnatal Depression Scale (EPDS) scores >13 in 6 months postpartum were predicted with ~90%, 80%, and 75% accuracy from third, second, and first trimester blood, respectively, while similar predictive accuracies.

Conclusions: We performed multiple imputation to create a risk phenotype which represents the actual counts of injection through the participants’ whole life. We imputed genotypes to perform GWAS on these 1187 individuals, each of whom has 9,456,841 SNPs. This huge information revealed that CEPI62 was probably associated with injection dosages. Prior research indicated that CEPI62 was associated with mitosis and retinal dysplasia. Further research is needed confirm the biological mechanism of CEPI62 and intravenous drug use.

Supported By: R01

Keywords: The AIDS Linked to the Intravenous Experience (ALIVE), Genetic epidemiology, Substance-related disorder, Multivariate Imputation by Chained Equations, Big Data Analysis

562. Big Data Analysis among Intravenous Drug Users: Genome-Wide Association Study Implicates Centrosomal Protein 162 (CEP162) as a Risk Factor in Injection Dosage

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Background: Using imputed genotype data, we performed a GWAS to identify risk variants for the injection dosage in a prospective cohort ascertained for drug injection.

Methods: The sample comprised 1187 individuals from the ALIVE cohort with available genome-wide SNP data. Using the semi-annual report from the ALIVE participants, we imputed the amount of their injection dosage, creating a quantity risk phenotype. We imputed genotypes, using the 1000 Genomes Project as reference and performed several procedures for quality control. We removed individuals with low genotyping rate. We excluded SNPs with MAF <0.01 and with >10% missing genotyping rate or Hardy-Weinberg test p-value <0.0001. Population stratification was accounted for by MDS. After frequency and genotyping pruning, 9,456,841 SNPs remained. After filtering, there were 901 males and 284 females. Multiple imputation was performed using Stata 12. GWAS was performed using PLINK.

Results: The top twenty SNPs were located on chromosome 2, 6, 11, 12, and 14. The most significant SNPs were found on chromosome 6 (rs17186320, β = -702, p = 1.56e-7) mapped to the centrosomal protein 162 (CEP162), which is associated with mitosis.

Conclusions: We performed multiple imputation to create a risk phenotype which represents the actual counts of injection through the participants’ whole life. We imputed genotypes to perform GWAS on these 1187 individuals, each of whom has 9,456,841 SNPs. This huge information revealed that CEPI62 was probably associated with injection dosages. Prior research indicated that CEPI62 was associated with mitosis and retinal dysplasia. Further research is needed confirm the biological mechanism of CEPI62 and intravenous drug use.

Supported By: R01

Keywords: The AIDS Linked to the Intravenous Experience (ALIVE), Genetic epidemiology, Substance-related disorder, Multivariate Imputation by Chained Equations, Big Data Analysis

563. Vasopressin (AVP) Gene Modulates Risk of Alcohol Dependence via Effects on Stress and Anxiety

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Background: Evidence suggests a role for AVP in addictive disorders given its ability to modulate stress responses and social interaction. In rats, elevated basal AVP levels are associated with increased alcohol consumption, while pharmacological antagonism of AVP receptors reduces alcohol consumption. AVP single nucleotide polymorphism (SNP) rs2282018 (A G) is associated with decreased AVP levels. We studied the relationship of rs2282018 to AD, and anxiety and stress responses that may mediate AD vulnerability.

Methods: 1549 subjects (1056 subjects with a lifetime DSM-IV diagnosis of AD and 493 controls) studied at the NIH Clinical Center in uniform screening protocols were genotyped using Illumina OmniExpress BeadChip Arrays. Gene effects on AD, cortisol and anxiety responses were tested in models using the three rs2282018 genotypes and the moderating variables gender
and ancestry. Distributions of gender and ethnicity were equivalent across cases and controls. **Results:** Homozygotes for the G allele of rs2282018 had a lower lifetime prevalence of AD (p=0.017), lower baseline anxiety levels (p=0.013), and lower prevalence of Anxiety Cluster disorders, as assessed by SCID interviews (p=0.035). The G allele was also associated with decreased basal serum cortisol levels (p=0.014), and this effect was more pronounced in women (p=0.008). **Conclusions:** Homozygosity for the G allele of AVP SNP rs2282018 may be protective for AD, possibly through decreased stress and anxiety responses. This effect is likely due to the reduction in AVP expression previously reported with this SNP. Although the effect exists in both genders, a gender-specific AVP receptor distribution likely accounts for the observed interaction. **Supported By:** NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH by the Doris Duke Charitable Foundation (Grant 2014194), the American Association for Dental Research, the Colgate-Palmolive Company, Genentech, and other private donors. For a complete list, visit the foundation website at http://www.fnih.org. **Keywords:** Vasopressin, Alcohol Addiction, single-nucleotide variation

564. Serotonin 1A Receptor Binding in Brain and Neurocognitive Characteristics of Mood Disorder Patients with and without Suicide Attempt

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**Background:** Suicidal mood disorder patients may differ from their non-suicidal counterparts in the associations among the components of multidimensional biological and neurocognitive data.

**Methods:** 115 subjects with Major Depression Disorder (MDD) or Bipolar Disorder (BD), 49 with past suicide attempts, underwent Positron Emission Tomography Imaging with [11C] WAY-100635, a 5-HT1A antagonist; binding was estimated in twelve brain regions. They also underwent a battery of neurocognitive testing with 76 standardized scores recorded. Correlations between region-specific binding and neurocognitive performance (NP) were measured adjusting for sex, and graphed using heatmaps. Multivariate analysis methods were used to compare groups by diagnosis and suicide attempt history.

**Results:** Association between 5-HT1A binding and neurocognitive performance was restricted to some brain regions and NP subscores, and differed based on diagnosis and suicide attempt history. Bipolar subjects more frequently displayed moderate to strong associations than MDDs (19% vs.11%), and suicide attempters had more than non-attempters (22% vs.10%). The Raphe Nucleus displayed a distinctive pattern of associations with NP scores compared to other regions. Average group differences in NP scores and binding were mostly not significant (one adjusted p<0.05). The correlation matrices between brain regions did not differ by diagnosis (p=0.64) or suicide attempt history (p=0.98), although the correlations between NP characteristics did (p=0.0001).

**Conclusions:** Multivariate associations between serotonin 1A receptor binding and neurocognitive characteristics show distinct patterns that go beyond group differences in average values between diagnostic groups. These findings might be exploited to build better and more sophisticated diagnostic and predictive models of depression and suicide attempt.

**Supported By:** 4P50MH090964

**Keywords:** PET imaging, neurocognitive outcome, suicide attempts, Mood disorders, multivariate analysis

565. Increased Plasma Levels of Circulating Cell-Free Mitochondrial DNA in Suicide Attempters - Associations with HPA-Axis Hyperactivity

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**Background:** Preclinical data suggest that chronic stress may cause cellular damage and mitochondrial dysfunction, potentially leading to the release of mitochondrial DNA (mtDNA) into the bloodstream. Major Depressive Disorder has been associated with an increased amount of mtDNA in leukocytes from saliva samples and blood, but no previous studies have measured plasma levels of free-circulating mtDNA in a clinical psychiatric sample.

**Methods:** In this study, free circulating mtDNA was quantified in plasma samples from 37 suicide attempters, who had undergone a dexamethasone suppression test (DST), and 37 healthy controls. We hypothesized that free circulating mtDNA would be elevated in the suicide attempters and associated with hypothalamic pituitary adrenal (HPA)-axis hyperactivity.

**Results:** Suicide attempters had significantly higher plasma levels of free-circulating mtDNA compared to healthy controls at different time points (pre- and post-DST) (all p-values <2.98E-12, Cohen’s d ranging from 2.55-4.01). Pre-DST plasma levels of mtDNA were positively correlated with post-DST cortisol levels (rho=0.49, p<0.003).

**Conclusions:** Suicide attempters may have elevated plasma levels of free-circulating mtDNA, which are related to impaired HPA-axis negative feedback. This peripheral index is consistent with increased cellular or mitochondrial damage. The specific cells and tissues contributing to plasma levels of free-circulating mtDNA are not known, as is the specificity of this finding for suicide attempters. Future studies are needed in order to better understand the relevance of increased free-circulating mtDNA in relation to the pathophysiology underlying suicidal behavior and depression.

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**Keywords:** Mitochondrial dysfunction, HPA axis, Suicide, Mood disorder, Cellular Aging
566. Acute Psychosocial Stress Impacts the Hemodynamic Response latency: A Novel Brain Phenotype that Relates to Markers of Acute and Chronic Stress

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Background: Stress has been shown to disrupt neurovascular coupling (NVC) in rodents via a GR-dependent pathway. The aim of this study was to investigate the dynamic effects of acute stress on peak-latency of the hemodynamic response (HRF-PL) in humans with fMRI and to explore how individual variance of this NVC marker relates to biological markers of acute and chronic stress.

Methods: FMRI (3T) data was acquired from healthy subjects that underwent an acute psychosocial stress paradigm (n 39) or a control intervention (n 20). A functional polygenic stress risk scores (PGRS) previously validated to regulation of GR-targets and risk for MDD. Voxelwise maps of HRF-PL were calculated by relating regression estimates of the HRFs 1st derivative to their canonical term of the cognitive regressor. HRF-PL of stress-related clusters were forwarded to correlation analyses with cortisol and the PGRS.

Results: The paradigm elicited a strong endocrine, heart-rate and subjective stress response (Cohen's d 0.9-1.8). A marked effect of stress on HRF-PL was detected in the right hippocampus (HC), bilateral insula (INS) and bilateral ventrolateral prefrontal cortex (VLPFC). Cortisol response was selectively predicted by the stress-related HRF-PL shift of the right HC cluster. Moreover, HRF-PL before stressor onset within the HC cluster showed significant correlations with the PGRS score. These correlations were restricted to HRF-PL and absent for classical amplitude-based responses.

Conclusions: We demonstrate that NVC markers of (para-)limbic cortex areas are reversibly altered by acute stress and that dynamics of this parameter relate to acute and chronic stress measures.

Keywords: Psychosocial Stress, BOLD fMRI, functional genomics, Methods

567. Cingulate Glutamate Relates to Symptom Improvement in Response to DBS in Treatment-Resistant Depression

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Background: Deep brain stimulation (DBS) of the subgenual cingulate (SCG) region is an investigational therapy for treatment resistant depression (TRD). Although the response rates in open label trials were promising, a sham-controlled trial was discontinued prematurely. Biomarker-based patient selection may improve the clinical outcome. Given previous reports of lower glutamate (glu) concentrations in anterior cingulate cortex (ACC) as an illness marker of depression, we investigated whether ACC glu relates to DBS response in patients with TRD, using in vivo proton magnetic resonance spectroscopy ((1)H-MRS).

Methods: Ten adults with TRD underwent (1)H-MRS using a short echo proton spectroscopy with a 10x35x20mm voxel placed in the pregenual-ACC, prior to receiving bilateral SCG-DBS. Depressive symptoms were assessed at pre-DBS baseline and six months post-DBS using the 17-item Hamilton Rating Scale for Depression (HDRS). We calculated glu concentrations in the ACC and correlated these with change in HRSD scores from baseline to six months.

Results: There was a significant reduction in HDRS scores at 6 months post-DBS from pre-DBS baseline (F = 19.841; p = 0.002). Lower baseline glu in ACC correlated to greater reduction in depressive symptoms following 6 months of DBS (r = −0.740, p = 0.014; 55% of the variance).

Conclusions: These preliminary results suggest that ACC-glu concentration may predict symptom improvement at 6 months in SCG-DBS. Lower glu levels could indicate reduced neuronal activity and minimal neuronal damage. ACC-glu levels might serve as a biomarker for response to SCG-DBS, but further work elucidating the imaging biomarkers of response is needed.

Supported By: AHS-CRIO

Keywords: Treatment Resistant Depression, Subgenual anterior cingulate cortex, Deep Brain Stimulation, Magnetic Resonance Spectroscopy, Glutamate

568. Separation of Key Metabolites of the Kynurenine Pathway by HILIC LC-MS/MS with Stable Isotope-Labeled Internal Standards

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Background: Tryptophan (TRP) is a critical amino acid for biological function, with over 95% being metabolized through the enzymatic kynurenine pathway. Studies suggest roles for kynurenine metabolites in neurological disease states, ranging from depression, schizophrenia to Alzheimer’s and Parkinson’s diseases. We developed a method to detect and resolve TRP, kynurenine (KYN), serotonin (5-HT), kynurenic acid (KYNA), 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), picolinic acid (PIC), quinolinic acid (QUIN), nicotinic acid (NIC), and nicotinamide (NTA). The method was developed to include kynurenine metabolites as well as resolve PIC from NIC, an isomer of PIC that is a source of nicotinamide adenosine dinucleotide (NAD) production alongside QUIN and NTA.
659. Copper Metabolism in Schizophrenia and Mood Disorders: Increased Ferroxidase Activity in Bipolar Disorder

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**Background:** Copper is a vital essential trace element which is involved with the development and maintenance of the brain. This study aims to assess serum copper levels, ceruloplasmin (CP) weight and ferroxidase activity in schizophrenia, bipolar disorder and major depression.

**Methods:** Patients with bipolar disorder (n=37), major depression (n=40), schizophrenia (n=36) and healthy controls (n=32) were enrolled into the study. Serum copper levels were determined by atomic absorption spectrophotometer, non-ceruloplasmin bound copper levels were determined by calculation and CP weight was measured with immunoturbidimetry. Serum ferroxidase activity was measured with an automated assay which measures oxidation rate of ferrous (Fe2+) iron ions to ferric (Fe3+) iron ions. One-way ANOVA and Kruskal-Wallis Test were performed for statistical analyses.

**Results:** There was statistically significant difference between groups in serum CP-ferroxidase activity (χ2=9.11, p=0.028). Post-hoc comparisons showed that the bipolar disorder group had significantly higher ferroxidase activity in comparison to the major depression (p=0.027), schizophrenia (p=0.019) and healthy control (p=0.012) groups. Ferroxidase activity was correlated with erythrocyte sedimentation rates in the bipolar disorder group (r=0.61, p<0.001) and C-reactive protein in the schizophrenia group (r=0.64, p<0.05).

**Conclusions:** Our findings are consistent with the fact that ceruloplasmin is an acute phase protein which is up-regulated by inflammation. Ceruloplasmin may alter several metabolic processes either with its ferroxidase or polyamine oxidase activities. Further studies may determine secondary metabolic changes upon up-regulated ferroxidase activity in bipolar disorder.

**Supported By:** Kafkas University Scientific Research Committee

570. Differential Association of Anandamide Levels with Binocular Depth Inversion Illusion Scores in Schizophrenia

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**Background:** Binocular depth inversion illusion (BDII) represents a naturally occurring illusion of visual perception that has been repeatedly linked to psychotic conditions and identified as a potential marker for at risk mental states. The endogenous cannabinoid system (ECS) plays a critical role in processes underlying perception and cognition. The endocannabinoid anandamide has been suggested protective in psychosis. Therefore, we explored associations between BDII and anandamide.

**Methods:** The BDII test was performed and blood and cerebrospinal fluid (CSF) was collected in 28 first-episode antipsychotic-naive schizophrenia patients (SZ) and 81 healthy controls (HC). The endocannabinoids anandamide and 2-arachidonoyl-sn-glycerol were quantified by LC/MS-MS. Multiple linear regression analysis (MLRA) using gender, age, body mass index and former cannabis use as covariates, was applied to explore interactions and associations between diagnosis and anandamide and BDII scores.

**Results:** BDII scores and CSF but not serum anandamide were significantly higher in SZ vs. HC. Associations between serum anandamide and BDII were significantly different between SZ and HC (PFWE=0.014; MLRA). A significant interaction term resulted from a SZ specific negative association between serum anandamide and BDII (BDII: P=0.006, β=−0.62; MLRA). For CSF anandamide, no significant interaction was found.

**Conclusions:** We found serum specific association differences of anandamide and BDII between SZ and HC. Here higher anandamide levels in serum were associated with lower BDII scores reflecting a regular mode of perception. This is in-line with its assumed protective role in SZ and it may be suggested the ECS has a disease intrinsic role for modulating visual perception in schizophrenia.

**Supported By:** 03-NV-003

**Keywords:** Anandamide, Endocannabinoids, Visual perception, First-Episode Psychosis (FEP), human study
571. Epigenetic Related mRNA Levels in Lymphocytes of Schizophrenic and Non-Psychotic Controls

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Background: Epigenetic dysregulation is involved in the molecular deficits in schizophrenia. Previous research has shown hypermethylation of GABAergic promoter gene and increases in DNMT1 and DNMT3A in post mortem brain of patients with SZ and in lymphocytes of patients with chronic schizophrenia (CSZ). We now report preliminary results on a larger set of epigenetic related mRNA’s in lymphocytes of CSZ.

Methods: CSZ (n=29) and non-psychotic controls (NPC) (n=31) subjects had lymphocyte pellet extracted from a blood sample by Ficoll gradient procedure. qPCR assays were used to measure epigenetically related mRNA’s – DNMT1, DNMT3A, TET1, TET2, TET3, BDNF, NR3C (glucocorticoid receptor), T-Cell Surface Glycoprotein CD4, CCR1, FRPRL3 (Fornyl Peptide Receptor). Patients were also evaluated with PANSS and MATRICS.

Results: CSZ showed significantly higher DNMT3A (P=0.048) than NPC Male CSZ showed significantly higher DNMT1 than NPC (P=0.014). Compared to NPC, CSZ subjects showed significantly higher levels of GABAergic enzymes measured by the GAD1 probe (P=0.030), higher levels of glucocorticoid receptor measured by the NR3C probe (P=0.006), and significantly lower levels of FRPRL3 (P=0.039). Higher levels FPRL3 and CD4 were moderately correlated with PANSS positive symptoms in CSZ (FPRL3 r=+0.43 P=0.019, CD4 r=+0.37 P=0.037). Higher DNMT1 and DNMT3A levels in lymphocytes of CSZ correlated negatively with scores n MATRICS battery (DNMT1 – attention/vigilance= r=–0.41, P=0.031, working memory= r=–0.37, P=0.048, composite score r=–0.36, P=0.063).

Conclusions: CSZ demonstrate differences in epigenetically related mRNA’s in their lymphocytes. In CSZ higher levels of DNMT were related to poorer cognitive performance and higher levels of immunological related mRNA to greater positive symptom scores.

Supported By: NIMH
Keywords: Adenine, schizophrenia, DNA methylation, mRNA

572. Cannabis Use and Matrix Metalloproteases in Schizophrenia

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Background: The pathophysiology of schizophrenia is unknown. One reason for this may be the heterogeneous nature of the illness. Defining and examining homogenous subgroups may provide an opportunity to increase the signal to noise ratio in pathophysiological studies. A significant body of literature suggests that adolescent cannabis use is associated with developing schizophrenia. Interestingly, this group of individuals is reported to have a distinct profile of symptoms – less impairment in cognitive function, more severe psychosis and worse outcomes with continued cannabis use. This may suggest that heavy adolescent cannabis use is associated with a schizophrenia subgroup.

Methods: We assembled a human post mortem cohort of dorsolateral prefrontal cortex tissue from cases of schizophrenia with and without ACU (n=10/group). Whole transcriptome sequencing was conducted followed by group comparison, co-expression network and gene-set enrichment analyses.

Results: 1851 genes are differentially expressed in between the two schizophrenia groups. The most highly differentially regulated gene is ADAMTS9 (p = 8.49 x 10−12), a member of the ADAMTS (A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif) family of zinc metalloproteases. ADAMTS1, 6, and 7 were also significantly different between the 2 groups. ADAMTS9 localizes to chromosome 3p14, a region linked to schizophrenia and is involved in cleaving chondroitin sulphate proteoglycans, core components of perineuronal nets that are reduced in schizophrenia.

Conclusions: Our human post mortem findings suggest that adolescent cannabis use is associated with changes in matrix metalloproteases that may contribute to disruption of perineuronal nets in schizophrenia.

Supported By: NIMH
Keywords: Adolescence, marijuana, DLPFC, Human Postmortem Brain, RNA sequencing

573. Evidence of both Systemic Inflammation and Neuroinflammation in Patients with Chronic Widespread Pain

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Background: Central hyperexcitability, impaired top-down modulation and chronic inflammation probably plays a role in the pathophysiology of chronic widespread pain (CWP). On the basis of both animal experiments and humans studies involving the analysis of cytokines and other inflammation-related proteins in different body fluids, neuro-inflammatory mechanisms are considered to be central to the pathophysiology of many chronic pain conditions. However, previous human plasma/ serum and/or cerebrospinal fluid (CSF) cytokine studies have looked only at a few predetermined cytokine candidates and not the overall pattern of neuro-inflammation.

Methods: We used a new multiplex protein panel enabling simultaneous analysis of 92 inflammation-related proteins in CSF and plasma from 40 CWP patients and 10 healthy Controls. All patients were diagnosed by a specialist in rheumatology and had no major somatic or psychiatric comorbidity.

Results: Using multivariate data analysis by projection, we found evidence of both neuro-inflammation (CSF) and chronic systemic
inflammation (plasma). Two groups of proteins (one for CSF and one for plasma) were highly discriminating between patients and controls while four proteins were important for group discrimination both in CSF and plasma (CXCL5, LAPTFG-beta-1, CXCL5, MCP-2). There were further high levels of CSF chemokine CX3CL1 (fractalkine) and IL-8 both in CSF and plasma.

**Conclusions:** This is the first extensive inflammatory profile described for CWP patients. Hence, CWP seems to be characterized by objective biochemical and neuro-immunological alterations, and the lingering characterization of its mechanisms as essentially idiopathic or even psychogenic should be seen as definitively outdated.

**Supported By:** Inven2 Inc (Oslo University Hospital); Uppsala Berzelii Technology Centre for Neurodiagnostics; The Swedish Research Council.

**Keywords:** Cytokines and Chemokines, chronic pain, Neuroinflammation, immunoinflammation, cerebrospinal fluid

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**574. Synthetic Cannabinoid Use in Relation to Psychosis: Evaluation of the Role of Stress and Immune Systems**

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**Background:** Synthetic cannabinoids (SC) are efficient cannabinoid receptor agonists. There is increasing evidence of the association between use of SCs and psychosis. However these studies are mostly limited to self-report evaluations, and there is lack of studies on the interaction of immune and stress bio-markers with psychosis in SC users.

**Methods:** The first phase of our project was a retrospective study of the potential association between self-report SC use and psychosis. The second phase is a cross-sectional study of patients with psychotic symptoms admitted to an inpatient unit over six months. Blood and urine samples were obtained for toxicology, cortisol and interleukins levels. A comprehensive psychiatric evaluation was conducted to evaluate clinical profiles. Regression analyses were performed for the association between SCs use with psychosis and its interaction with bio-markers.

**Results:** The data from the first phase verified a significant association between self-report SC use and psychosis compared to cannabis (Odds ratios 4.35 and 2.64, respectively). Preliminary results from the second phase demonstrate similar demographic factors and SC use among subjects. Life history of SC use was reported in 25% and cannabis in 62% of participants. Both natural and synthetic cannabinoid users had less positive symptoms and more negative symptoms of psychosis, compared to non-users. We will present results from the toxicology, stress and immune markers in association with clinical symptoms.

**Conclusions:** There is little known about the psychiatric profile of psychotic patients with SC use. This study would provide information about the specific SCs use in association with psychosis severity and related factors.

**Supported By:** Icahn School of Medical Sciences at Mount Sinai

**Keywords:** Cannabis, synthetic cannabinoid, Psychosis, Stress, Immune System

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**575. Resiliency is Associated with Reduced Activation within the Retrosplenial Cortex and Secondary Motor Area for Individuals with PTSD During Anticipation of a Negative Event**

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University of Arizona

**Background:** Individuals with post-traumatic stress disorder (PTSD) often engage in avoidance behaviors to minimize the pain of emotionally reliving the distressing experience. The retrosplenial cortex (RSC), strongly linked to episodic memory retrieval, and the supplemental motor area (SMA), responsible for internally driven action selection, may be implicated as important neurobiological components of this coping mechanism. We hypothesized that among participants with PTSD, greater psychological resilience would be associated with reduced responsiveness within regions relevant to self-relevant processing during a task involving anticipation of a negative image.

**Methods:** Eighteen participants (10 males, mean age=30.1), who met DSM-V criteria for PTSD, were administered an anticipation task during functional magnetic resonance imaging (fMRI) and then completed the Connor-David Resilience Scale (CD-RISC). After controlling for symptom severity (i.e., Clinician-Administered PTSD Scale), we conducted a whole-brain regression analysis within Statistical Parametric Mapping (SPM12) to investigate the association between activation (anticipating negative images versus baseline involving no anticipation) and CD-RISC scores.

**Results:** Participants who reported higher resiliency were found to have significantly less activation in the RSC (236 voxels, p<0.001, FDR corrected), SMA (144 voxels, p=0.005, FDR corrected), and medial somatosensory cortex (209 voxels, p=0.001, FDR corrected) during the anticipation of negative images.

**Conclusions:** More resilient individuals with PTSD engaged their RSC and SMA less when anticipating negative events, suggesting a potential neurobiological substrate of resilience in this population. These findings may have important implications for developing targeted interventions that focus on reappraising negative stimuli, rather than utilizing avoidance techniques.

**Supported By:** Department of Defense (DoD)

**Keywords:** PTSD, fMRI, Resilience, Retrosplenial Cortex (RSC), Secondary Motor Area (SMA)
576. Accelerated Neurodegeneration: Effects of Cumulative Trauma Exposure and Chronic Posttraumatic Stress Disorder (PTSD) in Relatively Young Combat Veterans

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**Background:** We previously published that combat veterans with PTSD (CV+PTSD) compared to healthy combat veterans (HCV) had significantly reduced gray matter volume (GMV) of olfactory cortex that was inversely related to burning odor sensitivity. Given that olfactory deficits (smell identification) are an early symptom of neurodegenerative disorder, and that some consider PTSD a disorder of accelerating aging, we sought to examine olfactory GMV and smell identification as a function of age in combat veterans with and without PTSD.

**Methods:** In this preliminary, cross-sectional study, 20 CV+PTSD (Age: M=30.4, SD=8.4) and 25 HCV (Age: M=30.8, SD=7.1) underwent a full clinical/trauma evaluation, standard smell identification testing, and a structural MRI exam.

**Results:** Of all variables including age, the only predictor of GMV in olfactory cortex of HCV was trauma load, quantified as the number and frequency of different traumatic event types (F1, 18= 12.5, p<.01). As trauma load increased, GMV of piriform cortex decreased (r=-.48, p=.01). Significant Diagnosis X Time (post-trauma) interactions revealed that the decreased olfactory GMV and impaired odor identification previously reported in CV+PTSD was driven primarily by the older veterans who had been ill the longest (ps<.05).

**Conclusions:** The current results demonstrate an association between trauma load and reduced olfactory GMV, an effect that may be magnified, and accompanied by impaired function, with repeated stressor-related events. Combined with our previous findings, we hypothesize that specific odor sensitivities may predict early and accelerated neurodegeneration across a spectrum of psychiatric and neurologic disorders.

**Supported By:** K01MH090548

**Keywords:** Trauma Exposure, PTSD - Posttraumatic Stress Disorder, Structural MRI, Gray Matter Volume, olfaction

577. Lifespan Gyrification Trajectories of Human Brain in Healthy Individuals and Patients with Major Psychiatric Disorders

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**Background:** Cortical gyrification of the brain represents the folding characteristic of cerebral cortex. Human gyrification trajectory from childhood to old age is unknown. Studies have shown regional gyrification alterations in patients with major psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ). However, it is unknown whether the lifespan trajectories of gyrification were altered in these patients.

**Methods:** We investigated the gyrification indices (GI; a quantitative representation of gyrification) of 881 subjects using the structural brain images in three independent cohorts. We fitted the GI with ten mathematical functions of age using within and cross dataset validations, and selected the function with the least mean standard error. The GI trajectories of healthy subjects and patients with major psychiatric disorders were fitted with the selected function, which were evaluated with the Pearson’s correlation and bootstrapping techniques.

**Results:** Healthy GI trajectory could follow a logarithmic function of age. The estimated GI of HS correlated with the measured GI (r=0.75; p<0.0001), accounting for 56.4% of total variance. The estimated GI accounted for 54.8% (r=0.74), 60.9% (r=0.78) and 33.8% (r=0.58) variance of MDD, BD-I and SCZ patients, respectively (all p<0.0001). GI trajectories of the BD-I and SCZ patients were deviated from the healthy one.

**Conclusions:** We discovered that the gyration trajectory during normal development and aging was not linear. We also found that the gyration trajectories of patients with MDD, BD and SCZ were deviated from that of healthy subjects during adulthood, indicating altered aging in the brain with these disorders.

**Keywords:** Gyrification, Brain Development and Aging, Major Depressive Disorder (MDD), Bipolar Disorder, Schizophrenia

578. Salience, Frontoparietal and Default Mode Network Alterations in Obsessive-Compulsive Disorder: A Meta-Analysis of Resting-State Functional Connectivity

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**Background:** Obsessive-compulsive disorder (OCD) has been linked to aberrant connectivity within and between large scale brain networks. Specifically, intrinsic functional connectivity (IFC) of ongoing brain activity has been shown to be aberrant in OCD. However, a consistent pattern of dysconnectivity has not yet been established due to the variability of the methods, and patient heterogeneities.

**Methods:** Meta analysis was performed on publications comparing seed-based whole brain resting state functional connectivity between OCD patients and healthy controls. 18 studies (541 patients, 572 controls) were included. Coordinates of seeds and between group effects were extracted. Seed regions were grouped into 7 predefined intrinsic brain networks. Multilevel kernel density analysis was conducted for each seed network in order to retrieve brain regions in which OCD was linked to consistent or specific hyper- and hypoconnectivity.

**Supported By:** K01MH090548

**Keywords:** Obsessive-compulsive disorder, Frontoparietal, Default Mode Network, Meta-Analysis, Seed-based, Resting-State Functional Connectivity
Results: Regarding patients with OCD, we found a consistent pattern of hypoconnectivity within the frontoparietal and default mode network. Hypoconnectivity was also found for between-network fIC, namely for frontoparietal and salience network, peaking in the supramarginal gyrus, and frontoparietal and limbic network, peaking in the nucleus accumbens.

Conclusions: This meta-analysis provides evidence for consistent alterations of brain networks and their connectivity in OCD, specifically for a reduced within-network connectivity in frontoparietal and default mode network, and a reduced between-network connectivity focused mainly on the frontoparietal and salience network. Disruptions in these networks might lead to the underlying symptoms of OCD.

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Keywords: Resting state fMRI, Functional connectivity, Brain networks, salience network, Obsessive Compulsive Disorder (OCD)

579. Region Specific Metabolic Correlates Contribute to Gene and Sex Relationship of Transitional Anxiety Phenotypes

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Background: Dysregulation of GABAergic system was shown in anxiety, and inhibitory/excitatory homeostasis in cortico-limbic structures such as anterior cingulate cortex (ACC) was depicted crucial for affective regulation. Factors contributing to development and higher prevalence in women are however not known. Thus, we investigated effects of GAD65 polymorphism, a GABA synthesizing enzyme and sex on intrinsic brain activity and inhibition/excitation balance in pregenual (pgACC) and mid cingulate (aMCC). Furthermore, we explored relationship to harm avoidance (HA), behavioral phenotype of anxiety.

Methods: 105 healthy subjects (45 females, 40 G-carriers, age= 27.07 ±6.75) completed resting state fMRI, magnetic resonance spectroscopy (MRS) in 7T scanner, where GABA and glutamate (Glu) were measured, and HA questionnaire. Gene and sex interaction were analyzed with ANOVA for both local ACC brain activity and GABA/Glu levels. Further mediating effects of the regional GABA/Glu on a gene-HA relationship was explored with relevance to sex. Statistics was set at p<0.05, when appropriate corrected for multiple comparisons.

Results: We found increased intrinsic activity and decreased inhibition/excitation balance for the AA variant in pgACC, which, for GABA/Glu was driven by genotype difference in females. Furthermore, pgACC GABA/Glu in females was negatively associated with HA. Lastly, there was an effect of sex on the mediation model, with again significance in women.

Conclusions: Our results show that gene and sex are factors contributing to region specific functional and metabolic associates of circuits of affect regulation. The observed interaction could be the basis of female-bias of anxiety disorders.

Supported By: DFG (SFB 779)

Keywords: Inhibition/excitation balance, pregenual anterior cingulate cortex (pgACC), GAD65 polymorphism, sex differences, anxiety phenotypes

580. Glutamate in Medial Prefrontal Cortex: Associations with PTSD and Fear Extinction Recall

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Background: Posttraumatic stress disorder (PTSD) involves altered functioning of brain regions that mediate fear extinction recall, including the medial prefrontal cortex (mPFC). Glutamate metabolism has been linked to both neuronal function and emotional memory, yet there has been little investigation of in vivo glutamate in PTSD. This study examined whether mPFC Glu and extinction memory were associated with PTSD diagnosis and symptoms, and whether mPFC Glu correlated with individual differences in extinction recall.

Methods: 39 DSM-IV PTSD, 29 trauma-exposed non-PTSD (TENP), and 30 healthy control (HC) participants completed 3T magnetic resonance spectroscopy (MRS) and a two-day fear conditioning and extinction paradigm. 2DJPRESS MRS spectra were collected from a 2 X 2 X 2 mL mPFC voxel, and glutamate (glu) was normalized to creatine (Cr). Skin conductance responses (SCR) were recorded during fear conditioning and extinction learning on Day 1, and during extinction recall on Day 2.

Results: ANOVA identified a group difference in mPFC Glu/Cr (F(2,92)=3.35, p=.04), driven by significantly lower Glu/Cr in PTSD versus HC (p=.01). Extinction recall was not associated with diagnosis, but was significantly correlated with emotional numbing symptoms in PTSD patients. In the combined sample, Glu/Cr was positively correlated with extinction recall (r=0.29, p=.0089). Finally, using multiple regression, both PTSD diagnosis and extinction recall were statistically significant as concurrent predictors of Glu/Cr.

Conclusions: Lower in vivo mPFC glutamate may be a neural correlate of PTSD and individual differences in extinction memory. Patients with better extinction memory had greater emotional numbing symptoms, suggesting a relationship between preserved extinction and emotional over-modulation.
581. The Default Mode Network in Posttraumatic Stress Disorder (PTSD): A Data-Driven Multimodal Approach

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Background: The default mode network (DMN) has been increasingly demonstrated to play a critical role in various brain functions. Alterations in DMN connectivity have been repeatedly associated with psychopathology, including posttraumatic stress disorder (PTSD). However, the network topology characteristics of DMN in PTSD have not been fully studied. Here we implement a data-driven approach based on graph theory, to investigate the DMN in a group of combat-exposed veterans.

Methods: Sixty-four veterans [PTSD: n = 34; combat control (CC): n = 30] completed high-resolution structural magnetic resonance imaging (sMRI) for accurate spatial localization, 2 runs of resting state functional connectivity MRI (rs-fcMRI), and diffusion MRI (dMRI) with 128 directions for tractography. Based on previously validated methods, we constructed 64 x 64 connectivity matrices per subject per modality (rs-fcMRI or dMRI) representing cortical DMN nodes.

Results: In the rs-fcMRI analysis, we found reduced functional integration within DMN in veterans with PTSD as evident by increased characteristic path length (p < 0.009) and reduced global efficiency (p < 0.004). The DMN in PTSD was also characterized by reduced local efficiency (p < 0.007) and clustering (p < 0.011). The dMRI results will be added at the time of poster presentation.

Conclusions: Using a data-driven approach, this study provides evidence of weakened functional connections within the DMN associated with PTSD. It remains to be demonstrated whether this functional DMN dysconnectivity is paralleled by structural alterations. Future longitudinal studies may utilize this data-driven approach to investigate the role of DMN disturbances in the development of the disorder or in its response to psychotherapeutic and pharmacological treatments.

Supported By: NCPTSD

Keywords: Default Mode Network, PTSD, graph theory, Resting state fMRI, diffusion MRI

582. Functional Connectivity Changes following Repetitive Transcranial Magnetic Stimulation (rTMS) in Individuals with Generalized Anxiety Disorder

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Background: Improved treatments for generalized anxiety disorder (GAD) are needed as many patients do not benefit from currently available therapies. We previously showed that low-frequency (1Hz) rTMS to right dorsolateral prefrontal cortex (rDLPFC) improves GAD symptoms. To explore rTMS treatment mechanisms, we present data here on pre-to post-treatment neural network functional connectivity (FC) changes.

Methods: Thirty-one adults with GAD and 20 matched healthy controls (HC) performed an fMRI task entailing decision-making under uncertainty. Participants predicted which of two cards would be drawn, with trials presented in Win or Lose blocks (75% of choices were either correct or incorrect, respectively). A patient subsample enrolled into an RCT of daily (5/week) active- (n = 9) versus sham (n = 7) rTMS for 6 weeks using the NeuroStar TMS Therapy System. Connectivity analysis included key emotion and decision-making networks regions-of-interest: dorsal and subgenual anterior cingulate cortex (dACC and sgACC), DLPFC, anterior insula (AI) and amygdala.

Results: Group (GAD/HC) by Condition (Win/Lose) interaction was found in the FC of dACC-right amygdala, dACC-sgACC, sgACC-right AI, dACC-right AI and dACC-left AI (pFDR < .05). Only dACC-sgACC showed a pre- to post-rTMS effect, with decreased positive FC post-treatment in active rTMS only (d = 1.4) during Lose. FC was ‘normalised’, as GAD, but not HC, showed significant positive FC at baseline. Pre-to-post FC changes positively correlated with anxiety, depression and worry symptoms improvements (r = 0.6, 0.6 and 0.5, respectively). The preliminary results indicate that rDLPFC-targeted rTMS modulates FC in GAD patients with implications for the development of improved personalized treatments.

Supported By: Hartford HealthCare Research Funding Initiative; Neuroethics

Keywords: Generalized Anxiety Disorder, rTMS, sgACC, dACC, fMRI

583. Computational Modeling of Fear Extinction Learning in PTSD: Cognitive and Neural Mechanisms

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Background: Recent advances in reinforcement learning models promise to enhance our understanding of cognitive processes underlying fear learning and guide treatment
584. Affective Cortico-striato-thalamo-cortical Functional Connectivities in Drug-naive Patients of Obsessive-compulsive Disorder

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Background: Dysfunction of affective CSTC loops, which encompassed orbitofrontal cortex(OFC), anterior cingulate cortex (ACC), ventral striatum and thalamus, has been implicated in neuroimaging pathological of obsessive-compulsive disorder(OCD) in recent studies. Regions in the loops play an important role in motivation, inhibition and behavior planning associated with symptoms of OCD. But results within the loops were inconsistent and even in contrast. Examination of drug-naive and no comorbidity patients with OCD might help avoiding some potential confounding factors.

Methods: Thirty-seven non-medicated OCD patients and 37 health controls (matched for age and gender) received the resting state functional-connectivity MRI (rs-fcMRI). Functional connectivities of the six striatal seed regions of interest (ROIs) to the whole brain were calculated between groups.

Results: Compared to health controls, functional connectivities with the ventral striatum were significantly reduced (p<.05) in the OFC (BA11), ACC(BA30) and thalamus. Besides, ventral striatum in right hemisphere also showed increased connectivities in calcarine, lingual gyrus and fusiform in occipital lobe.

Conclusions: Contrary to studies in patients on medication, our findings revealed the hypoconnectivity in affective CSTC loops, which may provide a more reliable evidence for the neuroimag pathological in OCD. Besides, our results suggest that OCD patients have abnormal connectivities other than CSTC circuits.

Supported By: National Natural Science Foundation of China (81371486)

Keywords: Obsessive Compulsive Disorder (OCD), rsfMRI, Functional connectivity, Ventral Striatum, Orbital Frontal Cortex

585. The Effects of Psychotherapy on Amygdalar Sub-regional Functional Connectivity in PTSD

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Background: Posttraumatic stress disorder (PTSD) displays altered resting state functional connectivity (rsFC) of the amygdala and its subregions. The basolateral amygdalar subregion (BLA) receives cortical inputs while the centromedial amygdalar subregion (CMA) sends outputs to various targets. We sought to understand how exposure therapy, a first-line treatment for PTSD, might differentially alter rsFC of these functionally distinct amygdalar subregions.

Methods: Individuals with PTSD were randomized to immediate prolonged exposure (PE) treatment (N=36) or to waitlist (N=30) and underwent resting state fMRI prior to treatment/waitlist and again one month following the end of treatment (or a comparable time period for waitlist). The rsFC from BLA and CMA seeds was assessed in relation to BLA and CMA targets in PTSD and in 37 trauma-exposed healthy controls (TEHCs) at baseline. Linear mixed models were used to assess treatment-related changes.

Results: Individuals with PTSD had lower BLA rsFC to CMA targets at baseline, which was due to abnormally elevated BLA rsFC to CMA targets in TEHCs relative to both PTSD patients and 31 trauma-naive healthy controls (NTHCs). Treatment selectively increased BLA rsFC to CMA targets, such that treated patients at post scan no longer differed from TEHCs but showed elevated BLA rsFC to CMA targets relative to NTHCs.

Conclusions: Exposure-based psychotherapy for PTSD alters amygdalar subregional rsFC such that treated patients
develop a distinct TEHC-like connectivity pattern that distinguishes them from NTHCs. Thus, elevated BLA rsFC to CMA targets may be a compensatory adaptation that promotes cessation of traumatic stress symptoms.

**Supported By:** RO1MH091860

**Keywords:** Amygdala, Basolateral amygdala, PTSD - Posttraumatic Stress Disorder, Resting state functional connectivity, Neuroimaging

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**586. Using Anxiety and Depressive Subtypes to Predict Electrocortical Processing of Distracting Pictures**

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**Background:** Patients with anxiety and depression share symptoms of emotion dysregulation and they may be more neurobiologically similar than different. For example, in healthy individuals, task-irrelevant emotional pictures presented under high compared to low working memory load elicit smaller late positive potentials (LPPs) - in other words, high working memory demands suppress attention towards distracting images in those without illness. However, this effect appears to be reduced in both anxious and depressed patients, suggesting increased distractibility by emotional images that is shared across disorders. Yet this work has not examined differences using empirically derived symptom profiles, which might help parse unique patterns of neural reactivity among anxious and depressed patients.

**Methods:** We used k-means clustering on scores from the Inventory of Depression and Anxiety Symptoms (IDAS) to identify 2 subgroups (n=39, “Anxious” and n=45, “Anxious Depressed”) within a group of 84 anxious and depressed patients before using these subgroups to assess the LPP to task-irrelevant negative and neutral pictures presented within a working memory task.

**Results:** The Anxious group showed a reduced effect of working memory load on the picture-elicited LPP (M=1.73 μV, SD=4.60), evident in comparison to both the Anxious Depressed group [t(82)=2.00, p=.05; M=4.20 μV, SD=6.58] and in comparison to a group of controls [n=29; t(66)=2.09, p=.04; M=4.19 μV, SD=5.09].

**Conclusions:** Alternative, empirically-driven means of classifying patients might be especially informative in revealing neurobiological differences between patients; moreover, anxiety and depression appear to exert opposing tendencies on the LPP.

**Supported By:** R01MH101497; K23 MH105553

**Keywords:** Event-related Potentials, Research Domain Criteria (RDoC), late positive potential, Anxiety, Depression

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**587. Brain Functional Mediators of Dimension-Specific Trait-State Relationships in Obsessive-Compulsive Disorder**

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**Background:** Neurobiological models of obsessive-compulsive disorder (OCD) poorly account for disorder's heterogeneity, which can result from the diversity of approaches used to evaluate the neural underpinnings of OCD symptom dimensions. Here we propose to identify the brain regions mediating the relationship between specific dimension scores and the actual expression of such symptoms.

**Methods:** Sixty-one patients with OCD and 28 controls underwent an fMRI exam divided in 4 resting-state like sequences. The presentation of aggressive/checking, contamination/cleaning, symmetry/ordering and general fear images. At the end of each sequence, participants rated their anxiety, intrusive thoughts and urge to ritualize. The DY-BOCS was used to assess the severity of major OCD symptom dimensions. Symptom-specific difference maps (symptom sequence vs. general fear) of voxel-wise fractional Amplitude of Low-Frequency Fluctuations were extracted, and we performed trait-brain-state mediation analyses to identify regions accounting for DYBOCS - post-sequence ratings relationships.

**Results:** Right angular gyrus activity significantly mediated the association between DY-BOCS symmetry/ordering scores and anxiety levels after the provocation of these specific symptoms (p=0.015). The correlation between contamination/cleaning scores and the intrusive thoughts evoked by contamination/cleaning images was mediated by the ventromedial prefrontal cortex (p=0.006), while the relationship of these same symptoms with urge to ritualize was partially mediated by neural activity in right fusiform gyrus and left insula (p=0.001 and p=0.007).

**Conclusions:** We provide, for the first time, a description of the brain regions underlying the expression of OCD symptoms in patients with different symptom profiles. Our results should foster the development of neurobiologically-informed OCD models accounting for disorder's heterogeneity.

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**Keywords:** Obsessive Compulsive Disorder (OCD), Functional Imaging, Symptom Dimensions, Symptom Provocation, Mediation Analysis

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**588. Working Memory (WM)-Related Activation as a Function of Pubertal Status and Sex in Children and Adolescents**

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**Background:** Working memory (WM) is a fundamental aspect of executive function that can be disrupted by various conditions such as ADHD, OCD and anxiety. Pubertal status and sex may also influence WM, but there is a lack of research comparing pubertal status and sex differences in WM. To address this gap, the current study compared WM-related activation in children and adolescents across pubertal status and sex using a computerized WM task with functional magnetic resonance imaging (fMRI). Results indicated that pubertal status and sex were significant predictors of WM-related activation, providing new insights into the role of these factors in WM performance.

**Supported By:** NIDCD RO1MH101497; R01 MH101497; K23 MH105553

**Keywords:** Working Memory, Pubertal Status, Sex, Children, Adolescents

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*S237*
Background: Sex differences in WM-related neural recruitment are well-documented in adults, but less studied in children. While developmental investigations have been published, pubertal stage per se is often not defined, hampering insights into how endocrine events shape brain changes during development. Here, we examined WM-related activation in children and adolescents pubertally staged by clinicians.

Methods: Typically developing children (N=20, age=8.73±0.38 years, all Tanner Stage (TS) 1, 60% girls) and adolescents (N=22; age=13.15±0.72 years; TS 2-5, median=4; 69% girls) performed an N-back WM task in a 3T MRI scanner. Whole-brain-voxel-wise data were analyzed using SPM5 for main and interaction effects of sex and pubertal status (p<0.001, uncorrected) with performance as a covariate of no interest. Data for the prepubertal children were tested separately for sex effects.

Results: There were no sex or age differences in WM performance or reaction time. However, boys activated, but girls deactivated the right hippocampus regardless of TS. Furthermore, children showed greater activation than adolescents in the left dorsolateral prefrontal cortex (DLPFC) regardless of sex. No sex-by-pubertal-stage interaction was observed in WM-related regions. In prepubertal children analyzed alone, boys showed greater activation than girls in the right inferior parietal lobule, medial prefrontal cortex and DLPFC. The hippocampal sex difference observed regardless of TS was also confirmed in the prepubertal children analyzed alone.

Conclusions: Previous findings in adults have demonstrated sex differences in WM-related brain activation. Our results in prepubertal children suggest that some sex differences in WM processing may be observable prior to the pubertal surge in gonadal sex-steroid secretion.

Keywords: Puberty, Working memory, DLPFC, Hippocampus, fMRI

590. Underconnectivity between Anterior and Posterior Default Mode Nodes in Individuals with ASD and Low Cognitive Ability

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Abstract:

Background: Developmental neuroimaging studies suggest that regional gray matter volume (GMV) peaks earlier in girls than boys. However, studies often assume that observed age-related sex differences coincide with puberty-related changes in sex hormones, and, there is little information about sex differences prior to pubertal onset. Here, we examined GMV in carefully screened children before and during well-delineated pubertal per se.

Methods: Seventy-eight typically-developing children and adolescents were categorized into two groups based on clinician-rated Tanner Stage (TS): pre-pubertal children (TS1, N=44, age=8.7±0.3yrs; 17 girls) and pubertal adolescents (TS2-5, N=34, age=13±0.7yrs; 16 girls). Multi-echo MPRAGE scans, acquired on a GE 3T MRI scanner, were processed to create normalized Jacobian-modulated GMV maps controlling for total brain volume. Data were analyzed in AFNI using a whole-brain, voxelwise multivariate model to test for sex and TS effects and for interactions.

Results: Controlling for TS, boys showed greater GMV than girls in the right orbitofrontal gyrus and cerebellum (p<0.05, FWE-corrected). Controlling for sex, pubertal adolescents showed greater GMV than did pre-pubertal children in the right amygdala (p<0.05, FWE-corrected). A sex-by-TS interaction was observed in the right insula (p<0.001, uncorrected): pre-pubertal boys had increased GMV compared to pre-pubertal girls (p<0.001), with a trend in the reverse direction for the pubertal cohort (p=0.10). The prepubertal sex differences in the insula were confirmed by post-hoc analysis including only these children (p<0.05, FWE-corrected).

Conclusions: These data identify sex differences in prefrontal GMV that are stable across puberty, puberty-related differences in amygdala that are independent of sex, and sex-by-TS interactions in insular cortex.

Keywords: Puberty, Voxel-Based Morphometry, Sex Differences
Background: Despite extensive funding for neuroimaging in Autism Spectrum Disorders (ASD) no published functional MRI (fMRI) studies incorporating exclusively Low Cognitive Ability (LCA-ASD) samples are available. Underconnectivity between default mode nodes (prefrontal cortex [mPFC], posterior cingulate cortex [PCC]) is well-replicated in studies including mostly High Functioning individuals with ASD (HFA). It remains unknown whether this finding generalizes to LCA-ASD.

Methods: T1-weighted anatomical and fMRI resting-state scans were acquired on a GE 3T scanner. 18 typically developing (TD, mean IQ=110), and 18 ASD individuals split into groups of 9 participants each (LCA: IQ85, mean=77; HFA: IQ100, mean=112) were matched on motion, age, and gender. Following standard preprocessing, mean-timeseries were extracted from seeds in mPFC and PCC and entered into a subject-level GLM. Whole-brain functional connectivity (FC) differences between the HFA-ASD vs. TD, LCA-ASD vs. TD, and HFA-ASD vs. LCA-ASD groups were examined using AFNI 3dtest++. Results were corrected for multiple-comparisons.

Results: Compared to the TD group, the HFA-ASD group showed no differences in FC for mPFC or PCC. The LCA-ASD group demonstrated hypoconnectivity between the mPFC and PCC compared to the TD group (mean z=−0.14 vs. 0.47, 95% CI [0.19; 0.48]) and compared to the HFA-ASD group (mean z=−0.12 vs. 0.41, 95% CI [0.20; 0.39]).

Conclusions: Results suggest that underconnectivity between default mode nodes previously reported for mostly high-functioning cohorts with ASD may be more pronounced in lower-functioning participants. It remains open whether the finding further generalizes to intellectually disabled children (IQ<70) who are difficult to study with fMRI.

Supported By: NIH: R01 MH081023; K01 MH097972; R01 MH101173

Keywords: Autism Spectrum Disorder, Resting state functional connectivity, Low cognitive ability, Default Mode Network, BOLD fMRI

591. Neural Reactivity to Monetary Reward in the School-Age Offspring of Depressed Parents

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Background: Identifying neural profiles that may predict future psychopathology in at-risk individuals is important to efficiently direct preventive care. Alterations in reward processing may be a risk factor for depression. The current study characterized the neural substrates of reward processing in children at low- and high-risk for depression due to maternal depression status.

Methods: Children (5.99-9.63 years) performed a monetary incentive delay task during fMRI acquisition. The analytical model focused on the Group (low-risk vs. high-risk) x Performance (hit vs. miss) x Condition (no reward vs. reward) interaction.

Results: Final analyses included data from 46 children. The whole brain analysis of the three-way interaction yielded five significant clusters: dorsolateral prefrontal cortex (xyz=50.35,15; F[1,44]=20.01, k=71), parahippocampal gyrus (xyz=−5.32,6; F[1,44]=14.88, k=46), superior temporal sulcus (xyz=−44,−41.9; F[1,44]=14.76, k=32), dorsal prefrontal cortex (xyz=−29.20,42; F[1,44]=13.57, k=25), and inferior temporal gyrus (xyz=59.56,−4; F[1,44]=13.68, k=21), ps<.05 corrected. All regions exhibited similar patterns, whereby the high-risk group showed blunted differences in activation between the no-reward and reward conditions when they hit the target, and differences in the opposite direction when they missed the target, compared to the low-risk group. Region-of-interest analyses indicated significant three-way interactions in the putamen (right: F[1,44]=4.10, p=.049; left: F[1,44]=5.02, p=.030), right nucleus accumbens (F[1,44]=4.84, p=.033), and left amygdala (F[1,44]=4.89, p=.032). The pattern of results was similar to that observed in the whole brain analysis; however, post-hocs did not survive correction.

Conclusions: Results suggest that children at high risk for depression are less able to flexibly and appropriately modulate their neural reactivity in response to different reward task conditions.

Supported By: University of Maryland (UMD) College of Behavioral and Social Sciences Dean’s Research Initiative Award (LRD), UMD Research and Scholars Award (LRD), National Science Foundation (NSF) in partnership with UMD ADVANCE Program for Inclusive Excellence Award (LRD), University of Maryland College of Behavioral and Social Sciences Dean’s MRI Research Initiative RFP Program (LRD).

Keywords: Maternal depression, Children, Reward, brain (or fMRI), Familial risk

592. GABA and Functional Connectivity in the Anterior Cingulate Cortex in Early Adolescence

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Background: Adolescence is a crucial period in the maturation of the human brain, with extensive synaptic pruning and myelination. However, little is known about the neurochemistry and functional connectome characteristics in vivo of the early stage of adolescence.

Methods: Here, we measured GABA levels and functional connectivity (FC) in the anterior cingulate cortex (ACC) in a subsample (N=231; age range: 10.5-12.4 years old) of a
large-scale population-based cohort study of early adolescence, using MR spectroscopy (MEGA-PRESS) and resting-state fMRI, respectively. We also investigated sex and age differences in GABA levels and FC, in addition to the association between GABA levels and FC, and the effect of sexual maturation on GABA levels and FC.

**Results:** Our study revealed three main findings. First, GABA levels were negatively correlated with age in girls. Second, seed-based FC of the ACC was negatively correlated with GABA levels. Third, GABA levels were higher, and seed-based FC of the ACC was weaker in the early sexual maturation group, adjusted for age.

**Conclusions:** Our results provide new insights into the dynamic metabolic and functional circuit maturation processes in the brain during early adolescence.

**Keywords:** GABA, Functional connectivity, Sexual maturation, MRI, Population neuroscience

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**593. Underconnectivity between Salience and Visual Networks is Associated with Symptomatology in Children with Autism Spectrum Disorders**

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**Background:** The anterior insular cortex (AIC), which is a part of the “salience network,” is critically involved during visual awareness, multisensory integration, and social and emotional processing. In children and adolescents with autism spectrum disorders (ASDs), evidence has suggested aberrant functional connectivity of AIC compared to typically developing (TD) peers. While recent studies have primarily focused on the connections between salience and social networks, much less is known regarding connectivity patterns between AIC and primary sensory regions, or how these patterns may impact autism symptomatology. To determine these links, the current investigation examined functional connectivity and behavioral measures in children and adolescents with ASDs.

**Methods:** Resting state functional connectivity fMRI data were acquired from participants with ASDs (n=36) and TD controls (n=38) matched on age (ASD mean=13.6y; TD mean=13.6y; range: 7-18y), motion, and nonverbal IQ. Measures of functional connectivity between salience and sensory network nodes were examined in ROI analyses, and correlated with autism symptomatology.

**Results:** Children with ASDs showed underconnectivity between left AIC and bilateral visual cortices (V1 and V2) compared to TD controls (ps<0.05). Moreover, these patterns of underconnectivity were positively correlated with the social awareness subdomain of the Social Responsiveness Scale in ASD (r(34)=0.32-0.39, all ps<0.05), such that decreased connectivity was associated with greater social impairment.

**Conclusions:** AIC mediates sensory perception and social awareness in typical development. Here, we demonstrate that disruptions in connectivity between AIC and vision in ASDs are associated with measurable impairments in social abilities, implicating deficient selection of salient information in ASD symptomatology.

**Supported By:** NIH: R01 MH081023, K01 MH097972, R01 MH101173

**Keywords:** Autism Spectrum Disorder, Resting state functional connectivity, fMRI, Vision, Salience

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**594. Impaired Motor Function and Atypical Motor Cortex Connectivity in Mature Adults with Autism Spectrum Disorder**

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**Background:** Impairments in fine and gross motor function, coordination, and balance are present early in development in children with Autism Spectrum Disorder (ASD) and persist into adolescence. Neuroimaging studies find atypical connectivity in cortical motor areas and the cerebellum. However, little is known about whether these differences in motor function persist or even worsen in mature adulthood and aging. This study examines motor performance and functional connectivity of the motor network in mature adults with ASD compared to typically developing controls (TD).

**Methods:** 16 adults with ASD (69% male; age 48.4±5.3 years) and 9 TD adults (100% male; age 50.0±7.7 years) completed the Bruininks Motor Ability Test (BMAT), a balance task, and a resting state functional MRI scan. Group differences on the motor and balance tasks, and in functional connectivity between ten anatomically defined regions of interest in the cerebellum, motor, and somatosensory cortex were assessed.

**Results:** Mature adults with ASD demonstrated significantly impaired motor function on the BMAT compared to TD adults (F=6.16, p=0.02), but did not differ on the balance task. Functional connectivity within motor and somatosensory cortex was reduced in mature adults with ASD compared to TD controls.

**Conclusions:** Mature adults with ASD experience impairment in motor function compared to TD adults, particularly on fine and gross motor tasks. This not only suggests that motor dysfunction persists beyond childhood, but also raises the concern that early functional deficits may be exacerbated as part of the normal aging process during which motor functions often decline.

**Supported By:** R01 MH103494

**Keywords:** Autism Spectrum Disorder, Resting state functional connectivity, motor cortex, Brain Development and Aging, motor skills
595. Tools Matter: Comparison of Two Surface Analysis Tools Applied to the Abide Dataset

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Background: The ABIDE 1 dataset is a premier example of shared neuroimaging data that promotes exploration of the factors related to the autism diagnosis relative to features accessible in structural and resting state functional MRI in over 1000 subjects. In this report, we use the ABIDE preprocessed data project to evaluate the extent to which the selection of software tool matters.

Methods: Using the analysis results available from the ABIDE Preprocessing project for the FreeSurfer 5.1 and 5.3, and ANTS results, we prepared a common results file (in csv format) that included the average thickness measure from each of the tools as defined over the regions of the Desikan-Killany-Tourville (DKT) atlas. Finally, we developed an R software package reader to ingest these files, and to perform a simple analysis of correlation between the various methods.

Results: The result of this effort is a GitHub repository, https://github.com/edickie/compare_surf_tools, which contains the summary data tables, R reader, sample R-based analysis examples, and the results of an analysis of the correlation of each of the anatomic regions. Across this set of regions, the mean and range of correlations observed (mean, range) was: 0.875, [0.7647, 0.9387]; 0.4316, [0.1945, 0.5912]; 0.4744, [0.1871, 0.6743], for FreeSurfer 5.1 and 5.3; FreeSurfer 5.1 and ANTS, respectively.

Conclusions: The FreeSurfer analysis in this data presents excellent inter-version (5.1 – 5.3) commonality. There are, however, substantial differences between the regional thickness results between the FreeSurfer and ANTS analysis. The conclusion is that the reporting of thickness measures should be qualified by software platform.

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Keywords: Brain Imaging, Big Data Analysis, reproducibility, structural analysis

596. Cortical Thickness Patterns in Anorexia Nervosa: Individualized Prediction Model and Correlations with Key Symptoms

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Background: Structural brain alterations have been demonstrated in patients with anorexia nervosa. However translating these results at the individual level is challenging. Individualized prediction models can overcome these limitations by providing for each subject an estimate of the probability that the subject has anorexia (AN) based on an individual scan.

Methods: Structural MR imaging scans were acquired from adult women with current restricting type anorexia nervosa (AN) (N=19), recovered patients with a previous diagnosis of anorexia nervosa, restricting type (AN-REC) (N=24), and healthy control women (CW)(N=24). A linear relevance vector machine learning algorithm was ‘trained’ to distinguish AN from CW using cortical thickness measurements from regions of interest derived from the literature. The resulting algorithm also estimated the probability of an individual subject belonging to either AN (1) or CW (0) groups.

Results: The model predicted whether a subject belonged to the AN or control group with 74% specificity and 74% sensitivity (χ²p=0.004). The features that contributed most to these predictions were the reduction of cortical thickness in the superior frontal gyrus, and the increase in cortical thickness in the orbitofrontal cortex and the insula. Predicted probabilities significantly differed between AN and CW (p=0.023) but no significant difference was found between AN-REC and CW. In addition, cortical thickness in the left medial orbital sulcus correlated with interoceptive deficits in AN.

Conclusions: Patterns of cortical thickness abnormalities in the frontal, orbitofrontal and insular cortex characterize patients with AN; these patterns disappear in AN-REC. Orbital cortical thickness is related to interoceptive deficits.

Keywords: Anorexia Nervosa, Cortical Thickness, Orbitofrontal, Insula, structural neuroimaging

597. Clinical Staging of Major Depression: Multimodal-Imaging Approach

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Background: MDD can be modeled as a ‘circuit disorder,’ with structural and functional imaging used to define brain network states that track with clinical symptoms and recovery. The contribution of illness stage in MDD has not been systematically factored into such models and MDD staging would consider clinical stages as a reflection of progressive or step-wise damage to the functional and structural integrity of the ‘MDD network’. We evaluated the disparate structural and functional connectivities (FA/FC) within MDD network.

Methods: Ninety-two subjects (treatment-naïve (n=23), treatment-responsive-recurrent (n=23), TRD (n=23)) and healthy-controls (n=23) were scanned. Multimodal-imaging data (T1/DTI/rsfMRI) was acquired, and standard preprocessing was applied. FA and FC in a TRD cohort compared to HC. Then,
the regional FA and FC findings identified in the TRD Vs HC group were sampled in the two additional cohorts of treatment-naïve and treatment-responsive-recurrent MDD patients to assess stage differences.

Results: By statistical comparison between TRD and HC, structural and functional results converge on two regions, medial-frontal and midcingulate. TRD patients showed lower FA in the cingulum-bundle and uncinate-fasciculus forceps-minor suggesting WM pathology in WM pathways impacted by DBS. In addition there was a functional disconnection between the SCC-mF, and SCC-MCC, just beyond the areas of FA abnormality. Moreover, the UF/FA FA and mF FC abnormalities were common to all depressed patients independent of stage; in contrast the CB FA and MCC FC findings were specific to TRD.

Conclusions: These results suggest differential abnormalities within components of the depression network that can distinguish ‘depression clinical stages’.

Supported By: NARSAD, R01

Keywords: Major Depressive Disorder (MDD), clinical staging, Multimodal neuroimaging, Brain networks

598. White Matter Correlates of Suicidal Ideation in Depressed Patients

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Background: Frontal-subcortical disconnection syndrome may be a component of depression psychopathology. As greater subjective depression and suicidal ideation (SI) may precede suicidal behavior including suicide attempts, examining white matter neural correlates of SI may improve our understanding of pathophysiology related to suicide risk.

Methods: Diffusion tensor imaging data were acquired in 56 subjects with major depressive disorder (MDD), aged 18-60 years. Beck Depression Inventory (BDI) and Beck Scale for Suicidal Ideation (SSI) scores were regressed with FA, controlling for age, sex, and years. Further study included examining white matter neural correlates of SI may improve 'depression clinical stages'.

Results: SI positively correlated with FA in 4 white matter clusters: left anterior corona radiata (ACR) (largest cluster; size = 1287), right superior corona radiata, right body of corpus callosum, and left inferior orbitofrontal white matter. SI did not correlate with BDI; therefore, FA changes are not mediating the subjective depression effect.

Conclusions: Increased structural connectivity in ACR, which links prefrontal regions with basal ganglia and brainstem, may be associated with SI in individuals with MDD, consistent with some, but not all, previous findings. The dual-process theory of higher cognition posits that prefrontal-subcortical connectivity may facilitate Type 2 thought processing (slow, capacity-limited, conscious, controlled thinking), overriding Type 1 processing (fast, high-capacity, non-conscious, automatic) that responds to emotion. MDD subjects with high SI may engage in more deliberate suicide attempt planning than impulsive, reactive brief suicidal ideators.

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Keywords: Diffusion Tensor Imaging (DTI), Tract Based Spatial Statistics (TBSS), Suicidal ideation, Depression

599. Cortical Excitability in Patients with Treatment Resistant Depression

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Background: Little is known about cortical excitability in patients with treatment resistant depression (TRD). This study aimed at assessing cortical excitability associated with TRD, using transcranial magnetic stimulation (TMS) combined with motor evoked potential (MEP) and electroencephalographic (EEG) recordings.

Methods: The study was approved by the Duke School of Medicine IRB. Ten depressed patients (7 female) and nine age-matched healthy volunteers (5 female) enrolled. Depressed patients met DSM-IV diagnostic criteria for MDD without psychotic features, and had an inadequate response to at least two antidepressants. Cortical excitability assessment consisted of: 1) Resting motor threshold (RMT); 2) Resting EEG recording with eyes open for 5 minutes; 3) Somatosensory evoked potential (SEP); 4) Paired-pulse TMS with interstimulus intervals (ISI) of 2, 3, 15, and 25 ms; 5) simultaneous TMS-EEG.

Results: Resting EEG showed a significant suppression of alpha power for the TRD group relative to controls at the parietal and occipital sites, but not at frontal cortex. SEP showed a diminution of the P30 component in TRD (p < .05). For paired-pulse TMS, there was a significant group-by-ISI interaction effect (p < .05); of interest, at 25 ms ISI, there was a significant reduction in MEP amplitude in TRD (p < .05), which indicates a lack of intracortical facilitation. The TMS-evoked potentials recorded at FCz (average reference) showed an elevation of the P30 component in TRD (p < .05). Finally, no difference in RMT was observed between TRD and controls.

Conclusions: Overall, TRD patients showed a general downregulation of cortical excitability in our battery of assessments.

Supported By: Jansen Research

Keywords: Treatment Resistant Depression, TMS-EEG, Excitability, quantitative electroencephalography (qEEG), Antidepressant
600. Resting State fMRI of Raphe Nucleus Activity following Ketamine
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Background: Serotonin (5HT) neurons in the dorsal raphe nucleus (DRN) are implicated in mood regulation. Established dynamic variability in 5HT activity requires exploration to determine its role in functional network connectivity. Resting state fMRI (rsfMRI) may become an avenue toward accessing DRN oscillatory characteristics in depression. In previous studies using this approach, acutely manipulating 5-HT function and mood with tryptophan depletion produced robust changes in DRN activity rhythms (band-limited spectral power, SP) and in functional connectivity (FC) between DRN and limbic regions. The present study investigated whether rapid mood changes induced by ketamine infusion also involved changes in DRN SP and FC.

Methods: Seven depressed participants (MADRS > 20) had a baseline rsfMRI scan immediately followed by ketamine infusion (5 mg/kg), a second scan 1h after the infusion and a third scan 24h later. FSL and MATLAB analyses used motion correction, ICA-based denoising, and manual selections of DRN, ventral tegmental area (VTA), anterior thalamus (AT), and other regions. Band-delimited filtering used wavelet transforms prior to determining SP and FC.

Results: 71% of patients had a robust mood improvement 1 hour post-infusion and 86% by 24h. DRN SP at .25-.125 Hz decreased markedly from baseline (3.4x10⁶) to 1h post-ketamine (1.9x10⁶; p=.05 non-corrected). DRN to AT FC at .06-.03 Hz increased significantly (Δz = .36, p=.04, corrected) from baseline to 1 h post-ketamine. Most FC changes between 1h and 24h post-ketamine involved frontal regions.

Conclusions: Ketamine infusion is associated with robust changes in DRN oscillations and FC and these may be involved in the observed rapid mood improvement.

Supported By: University of Arkansas for Medical Sciences Translational Research Institute

Keywords: Serotonin, Resting state fMRI, Slow wave oscillations, Dorsal Raphe, Ketamine

601. Identification of Limbic Fibers Crossing the Massa Intermedia using Diffusion Tensor Imaging
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Background: The massa intermedia or interthalamic adhesion spans between bilateral medial thalami; however, it is absent in up to 20-30% of individuals. Its significance, especially in regards to functional pathways has yet to be fully elucidated. Probabilistic diffusion tensor imaging (DTI) has recently been used to seed the lateral habenula (LHb) and define its afferent white matter pathway, the stria medullaris thalami (SM). We sought to determine if the massa intermedia serves as a commissure for crossing of limbic fibers.

Methods: Probabilistic DTI was performed on five consecutive patients who had presence of a massa intermedia as visualized on MRI. Manual identification of the LHb on axial T1 weighted magnetic resonance imaging (MRI) was used for the initial seed region for tractography.

Results: In all patients, the SM was reliably visualized. Evidence of bilateral SM projections from the left LHb were consistently present within the massa intermedia in patients with a greater proportion of fibers crossing midline in patients with larger massa intermedia diameters.

Conclusions: Evidence of crossing SM fibers within the massa intermedia as shown by probabilistic DTI provide new insight into its functional significance within the limbic system. Given its anatomic location as a potential commissural pathway between thalami, further studies are necessary to assess the implications of its presence or lack thereof within the limbic functional network.

Keywords: Thalamus and limbic regions, lateral habenula, stria medullaris, Diffusion Tensor Imaging (DTI), massa intermedia

602. PET Imaging of Individual Raphe Nuclei in Major Depressive Disorder: Physiologic Insight and Diagnostic Utility
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Background: Numerous Positron Emission Tomography (PET) studies in Major Depressive Disorder (MDD) have reported higher 5-HT1A autoreceptor binding in the raphe nuclei. However, the raphe nuclei contain several separate nuclei, and they may be differentially involved in disease. Using PET, we examined 5-HT1A binding in individual raphe nuclei to better understand serotonergic abnormalities in MDD.

Methods: A hybrid set-level technique was used on an average [11C]-WAY100635 PET image derived from 52 healthy controls to delineate three raphe nuclei: Dorsal Raphe (DR), Median Raphe (MR), and Raphe Magnus (RMg). This atlas image was nonlinearly warped to each subject (through an associated MRI) in a separate sample of 35 males (20 healthy controls, 15 MDD) who underwent [11C]-WAY100635 PET. Binding potential (BPF) in each nucleus was compared between MDD and healthy volunteers. To
603. Post-Treatment Changes in Hippocampus Metabolism and Diffusivity Assessed by PET/MR following Electroconvulsive Therapy

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Background: Major depressive disorder (MDD) is a prevalent illness with low response rates. Whereas electroconvulsive therapy (ECT) is often effective for patients with otherwise untreatable depression, its mechanism of action remains unclear. Recently, pretreatment amygdala and hippocampal volumes have been suggested as predictive factors of ECT response, as ECT has been hypothesized to exert a neuroplastic effect on the regions. We used simultaneous PET/MR to look at a variety of ECT-induced changes in the brain.

Methods: Six medicated, depressed participants were scanned before and after bilateral ECT treatment using PET/MR (Siemens Biograph mMR). Symptom severity was measured with the Hamilton Depression Rating Scale (HDRS). PET was performed using FDG. MR included MPRAGE and diffusion tensor imaging (DTI). PET data were used to estimate the metabolic rate of glucose (MRGlu). Mean diffusivity (MD) was calculated from the DTI data.

Results: All but one participant remitted. FDG-PET for both pre- and post-treatment is only available from 4 of the remitters. When normalized by cerebellum, hippocampus MRGlu increases following ECT (p < 0.052). Similar changes were observed in other brain regions such as dorsal raphe nuclei (p < 0.038). And as we previously reported that MD changes in the left hippocampus are linearly correlated with HDRS reduction (Pearson r = 0.88; p = 0.02).

Conclusions: Hippocampal mean MD reduction, an indication of neurogenesis, of the left hippocampus was also found to be correlated with HDRS reduction. Glucose metabolism was also found to increase in many regions of the brain including hippocampus.

Supported By: Dana Foundation and Brain & Behavior Research Foundation

Keywords: PET, Major Depressive Disorder (MDD), Serotonin 1A receptor, Neurophysiology, Neuroanatomy

604. Association between Major Depressive Disorder and the COMT Polymorphism as Assessed by Diffusion MRI

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Background: Catechol-O-Methyltransferase (COMT) is responsible for most dopamine degradation in the frontal cortex. Individuals with the COMT Val158Met polymorphism have higher synaptic dopamine than individuals with the val-allele. This observation has led to interest in the gene’s potential role in Major Depressive Disorder (MDD), particularly the hypothesis that individuals carrying the met-allele may be at a higher risk for MDD. Previous studies indicate significant differences in hippocampal and amygdala volumes across COMT genotypes in healthy controls.

Methods: We examined diffusivity in the amygdala, hippocampus and parahippocampus of 22 healthy controls and 45 MDD patients using diffusion tensor imaging (DTI). Our study examined 24 homozygous-val, 7 homozygous-met and 36 heterozygotes. Age correction was performed using linear regression.

Results: When comparing all individuals, no volumetric or diffusion differences were apparent across genotypes in any region. This persisted when comparing the control and MDD groups separately. Restricting the analysis to female participants, we observed several differences across genotypes. For depressed females, parahippocampal fractional anisotropy was bilaterally lower in homozygous-met individuals than val-carriers (p_left = 0.028; p_right = 0.01), although the result only attains statistical significance bilaterally when homozygous and heterozygous-val are considered a single population (p_left = 0.094; p_right = 0.044). For all female participants, mean diffusivity in the left parahippocampus was significantly higher in homozygous met individuals than val-carriers (p_left = 0.006; p_right = 0.832). This was observed when comparing MDD separately (p_left = 0.003; p_right = 0.850) as well as across the entire female population.

Conclusions: Our research has furthered the assumption of a sex-genotype interaction and possible differences across sex in MDD. In particular, COMT polymorphisms may predispose females to depressive symptomology.

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Keywords: Polymorphism, Depression, COMT Val/Met
605. Neuroimaging Phenotypes of CACNA1C rs1006737 in Adolescent Bipolar Disorder

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Background: The CACNA1C rs1006737 bipolar disorder (BD) risk allele has been implicated in brain structure differences in both BD and healthy control (HC) adults, including the ventromedial prefrontal cortex (vmPFC), ventro-lateral prefrontal cortex (vlPFC), anterior cingulate cortex (ACC), hippocampus, and amygdala. However, no prior study has examined associations between rs1006737 and brain structure in adolescents.

Methods: Ninety-one adolescents (14-20 years; 41 BD, 50 HC) underwent 3-Tesla Magnetic Resonance Imaging (MRI). T1-weighted images were processed on FreeSurfer. Regions of interest (ROIs) included vmPFC, vlPFC, ACC, hippocampus, and amygdala. Whole-brain analyses examined cortical thickness, volume, and area. General linear models included main effects of diagnosis and allele, and an interaction term, controlling for the age, sex, and total intracranial volume.

Results: ROI analyses found larger ACC volumes (p = 0.006, pFDR-corrected = 0.054, ηp² = 0.087) and areas (p = 0.002, pFDR-corrected = 0.018, ηp² = 0.111), and smaller vmPFC (p = 0.014, pFDR-corrected = 0.104, ηp² = 0.069) and vlPFC (p = 0.023, pFDR-corrected = 0.104, ηp² = 0.059) thicknesses, in BD versus HC adolescents, and a diagnosis-allele interaction for vlPFC volume (p = 0.040, pFDR-corrected = 0.18, ηp² = 0.049), whereby the risk (A) allele was associated with reduced vlPFC volume in HC, but increased in BD. Whole-brain analyses, corrected for family-wise error, found larger pars orbitalis, rostral middle frontal area, and inferior temporal cortex areas, but smaller transverse temporal cortex areas, in BD versus HC adolescents (p < 0.05), larger fusiform volumes and lateral orbitofrontal areas in risk allele carriers (p < 0.05), and no interaction effects.

Conclusions: The current study provides preliminary evidence for main and interactive effects of rs1006737 BD risk on adolescent brain structure. Further investigation of rs1006737 associations with other BD neuroimaging phenotypes are warranted.

Supported By: Ontario Mental Health Foundation
Keywords: Bipolar Disorder, Adolescents, Structural MRI, Inflammatory Markers, Genetic Variants

607. Internalizing Symptoms are Differentially Associated with Resting State Default Mode Connectivity in Youth with a History of Traumatic Brain Injury

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Background: Poor outcome following traumatic brain injury (TBI) in children and youth includes symptoms of mood and anxiety disorders. Resting state functional brain connectivity (RS-FC) associated with the default mode network (DMN) is altered following TBI and in internalizing disorders. This study aims to assess patterns of DMN RS-FC that are associated with symptoms of internalizing disorders in youth with and without a history of TBI.

Methods: In a large sample of youth (Philadelphia Neurodevelopmental Cohort) with and without a history of TBI, we compared levels of internalizing symptoms between groups...
(TBI=1251, NoTBI=7294). In a subsample of participants with high quality resting state fMRI data (TBI=311, NoTBI=2269) we compared DMN connectivity between groups and investigated if history of TBI modulated the relationship between DMN RS-FC and internalizing symptoms. 

**Results:** Participants with a history of TBI had higher levels of internalizing symptoms than those who did not have a history of TBI. In the subset of participants who underwent functional imaging, there was no difference in DMN connectivity between groups. TBI participants displayed differential associations between DMN connectivity and levels of internalizing symptoms such that lower levels of connectivity within the DMN predicted increased symptoms in youth without a history of TBI and lower levels of connectivity between the DMN and other resting state networks predicted higher levels of internalizing symptoms in youth with a history of TBI. 

**Conclusions:** These results suggest that differential variations in within and between network DMN connectivity are related to internalizing symptoms if there is a history of TBI. 

**Supported By:** SickKids Foundation; FedEx Catalyst Scholarship

**Keywords:** Mild Traumatic Brain Injury, Resting state functional connectivity, Mood disorders, Default Mode Network, Anxiety Disorders

### 608. Baseline Resting-State fMRI Biomarkers of Depression Response to DLPFC-rTMS: Different Patterns of Functional Connectivity Predict Response to 10 Hz rTMS and Intermittent TBS

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**Background:** Conventional rTMS for treatment-resistant depression (TRD) targets the dorsolateral prefrontal cortex (DLPFC) using 10 Hz stimulation over 37.5 minutes. Brief rTMS protocols, such as intermittent theta-burst (iTBS), could improve rTMS accessibility in TRD. However, it is not fully known what aspects of brain functional connectivity predict either treatment. The aim of this study is to identify the resting-state functional predictors of treatment response to 10 Hz stimulation and iTBS.

**Methods:** 330 TRD patients were randomized to one of two treatment conditions: 10 Hz or iTBS over the left DLPFC. Treatments occurred once daily for a total of 20–30 sessions. On MRI, patients underwent a T1 and 10-minute resting-state functional scan before and after treatment. In accordance with previous findings, we completed a seed-to-voxel-based approach using cortical and striatal seeds to determine functional connectivity predictive of treatment response in the two treatment conditions.

**Results:** In both treatment conditions, treatment response followed a bimodal distribution with distinct rTMS-responsive and non-responsive groups; outcome distributions showed no significant differences. Lower functional connectivity from the ventral striatum to the bilateral frontal pole predicted treatment response in one group, while in the other, lower functional connectivity from the left DLPFC to the left anterior cingulate cortex predicted treatment response.

**Conclusions:** It appears that cortico-cortico and cortico-striatal functional connectivity differentiates response to two different rTMS treatment protocols. This difference in predictors was evident despite very similar clinical outcomes. Further work will also characterize how functional connectivity changes in responders over the course of treatment in both groups.

**Supported By:** CIHR

**Keywords:** Treatment Resistant Depression, HF-rTMS, Resting state functional connectivity, Biomarkers

### 609. Cerebrovascular Reactivity is Associated with Cardiovascular Risk Factors and Cognition Among Adolescents

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**Background:** Cerebrovascular reactivity (CVR) is the vascular response to a vasoactive substance; lower CVR indicates worse cerebrovascular health. In adults, CVR is negatively correlated with cardiovascular risk factors (cvRFs; e.g. hypertension) and positively correlated with cognition in some studies. This study examines the association of CVR with cvRFs and cognition in adolescents with and without bipolar disorder (BD), a disease linked with early atherosclerosis.

**Methods:** CVR was measured using blood-oxygenation-level dependent fMRI at 3-Tesla, in total gray matter. Eighteen BD and 40 healthy control (HC) adolescents conducted six 15-second breath-holds, alternating with 30-second free-breathing intervals. Body mass index (BMI), waist circumference (WC) and blood pressure were used as cvRFs. A subsample (12 BDs and 25 HCs) conducted an Intra-Extra Dimensional Set shift (IED) and a Cambridge Gambling Task (CGT).

**Results:** CVR was significantly positively correlated with BMI and trended with WC in BD (r=.512, p=.03; r=.422, p=.09), but not HCs (r=.206, p=.20; r=.080, p=.64). No associations were significant for blood pressure. CVR was significantly negatively correlated with IED scores in HCs but not BDs. CVR trended with CGT scores for BDs (r=.518, p=.09), but not HCs (r=.085, p=.69).

**Conclusions:** This study found that the association of CVR with cvRFs and cognition differs for BD and HC adolescents. Reasons for this may include limited variability of cvRFs within the HC sample, medication effects, and/or disease effects. Larger, prospective studies are warranted to extend these findings and examine for symptom associations with CVR.

**Supported By:** Ontario Mental Health Foundation

**Keywords:** Cerebrovascular Reactivity, Bipolar Disorder, Adolescents, Vascular Risk, Cognition
610. Hippocampal Subfield Volumes in Children and Adolescents with Mood Disorders

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**Background:** Studies investigating hippocampal volume in patients with mood disorders have found global reductions compared to healthy controls. The hippocampus, however, consists of anatomically distinct subfields, and certain subfields may be more sensitive to volume reduction than others. Adult studies based on structural brain scans have reported that both patients with Major Depressive Disorder (MDD) and Bipolar Disorder (BD) have smaller hippocampal volumes in regions within the cornu ammonis (CA1 and CA4) and dentate gyrus (DG) compared to healthy controls. Subfield changes in pediatric patients with mood disorders, on the other hand, have not been extensively investigated. Thus, the current study, investigates differences in hippocampal subfield volumes in children with BD, MD, and healthy controls.

**Methods:** Magnetic resonance imaging scans were obtained for 57 children with BD, 30 with MDD, and 54 healthy controls. A novel automated segmentation method was then used to evaluate hippocampal subfield volumes.

**Results:** Children with BD were found to have significantly smaller volumes in the right CA1, CA4, and subiculum, as well as the granule cell layer (GCL), molecular layer (ML), and hippocampal tails. A negative correlation was found between illness duration and the volume of the right subiculum in BD.

**Conclusions:** The identified hippocampal subfields tend to be atypical while others are not, and the longer a patient has had BD, the more damaged the subiculum may be. Overall, these findings provide evidence for specific hippocampal subfield volume reductions in children and adolescents with BD and suggest progressive reductions over time.

**Supported By:** by NIMH grant R01 085667, The Dunn Research foundation and the Pat Rutherford, Jr. Endowed Chair in Psychiatry (Jair C. Soares).

**Keywords:** Brain Imaging, Pediatric Bipolar Disorder, Major Depressive Disorder (MDD), Hippocampal subfields

611. Individualized Prediction of Euthymic Bipolar Disorder and Euthymic Major Depressive Disorder Patients Using Neurocognitive scores, Neuroimaging Data and Machine Learning

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**Background:** Approximately 60% of bipolar disorder (BD) patients are initially misdiagnosed with major depressive disorder (MDD). It takes about 5-10 years for BD patients to get the right diagnoses. We propose a novel machine learning approach to distinguish euthymic BD patients and euthymic MDD patients using neurocognitive measurements.

**Methods:** A total of 24 euthymic BD patients, 24 euthymic MDD patients and 24 healthy controls (HC) all demographically matched were included in the current study. Participants performed the South Texas Assessment of Neurocognition to assess cognitive performance and scans. The least absolute shrinkage selection operator (LASSO) machine learning algorithm was implemented to identify a neurocognitive signature to distinguish individual euthymic BD patients from euthymic MDD patients.

**Results:** The LASSO algorithm identified individual BD patients from MDD patients with an accuracy of 67% and an area under the receiver operating characteristic curve of 0.667 (p=0.021). A multivariate pattern of neurocognitive abnormalities comprising of California Verbal Learning Test and the Identical Pairs Continuous Performance was relevant in distinguishing individual BD from MDD patients. Notably, BD patients were significantly distinguishable from both MDD patients and HC, whilst MDD patients were indistinguishable from HC in both scenarios.

**Conclusions:** Neurocognitive abnormalities can distinguish individual euthymic BD patients from euthymic MDD patients with significant accuracy. The predictive neurocognitive signature identified in the current study may be used to making individualized clinical inferences about patients with mood disorder.

**Supported By:** NIH R01 MH 085667, the Dunn Foundation and Pat Rutherford, Jr. Chair in Psychiatry at UTHealth to Jair C. Soares

**Keywords:** Machine learning, Bipolar Disorder, Prediction, Neurocognition, Brain Imaging

612. Hippocampal Subfield Volumes in Mood Disorders

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Background: Volume reduction and shape abnormality of the hippocampus have been associated with mood disorders, such as bipolar disorder (BD) and major depressive disorder (MDD). However, the hippocampus is not a uniform structure and consists of several subfields, such as the cornu ammonis (CA) subfields CA1–4, the dentate gyrus (DG) including a granule cell layer (GCL) and a molecular layer (ML). It is necessary to investigate the link between the in vivo hippocampal subfield volumes and mood disorders.

Methods: We used a state-of-the-art hippocampal segmentation approach on brain scans of 371 subjects (152 healthy subjects, 133 BD, and 86 MDD). For each hippocampal subfield, we used a general linear model to investigate the effect of diagnoses. Partial correlations were performed between the hippocampal subfield volumes and the illness duration and numbers of mood episodes in BD and MDD patients.

Results: BD patients, especially bipolar I disorder (BD-I) patients, had reduced volumes of hippocampal subfields, specifically in the left CA4, GCL, ML, and both sides of hippocampal tails, compared to healthy subjects and patients with MDD. The volumes of the right CA1, ML and Sub decreased as the illness duration increased, and the volumes of both sides of the CA2/3, CA4 and hippocampal tails had negative correlations with the number of manic episodes in BD-I.

Conclusions: These results indicated that among the mood disorders the hippocampal subfields were more affected in BD-I than bipolar II disorder and MDD, and manic episodes had focused progressive effect on the CA2/3, CA4 and hippocampal tails.

Keywords: Hippocampal subfield, Major Depressive Disorder (MDD), Bipolar Disorder, MRI, Neuroprogression

613. Obesity-Related Thinning in the Frontal Cortex in Patients with Bipolar I Disorder: Correlations with Functioning

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Background: Obesity is associated with a more severe course in bipolar disorder, but the mechanism of this association is still unknown. We assessed obesity-related alterations in cortical thickness in the frontal cortex and global functioning in obese and normal weight patients with bipolar I disorder.

Methods: We extracted cortical thickness measurements in frontal regions in obese (N=40) and normal weight (N=29) subjects with bipolar disorder, and in obese (N=30) and normal weight (N=72) controls.

Results: The left orbital part of the inferior frontal gyrus (p=0.004) and the right orbital part of the inferior frontal gyrus (p=0.044) showed reduced cortical thickness in the bipolar group with obesity compared with the healthy control group with normal weight. The finding was still significant after controlling for age, sex and treatment with atypical antipsychotics, lithium, mood stabilizers and antidepressants. Furthermore, cortical thickness in the left orbital part of the inferior frontal gyrus correlated with the global assessment of functioning scale (GAF) across all groups (rs=0.2; p=0.008).

Conclusions: Reduced cortical thickness in the frontal cortex is associated with morbid obesity and bipolar disorder, and directly correlates with GAF.

Keywords: Obesity, Bipolar Disorder, Cortical Thickness, Inferior frontal gyrus, Brain Imaging

614. Paradoxical Increase in Corpus Callosum Volume in Adult Females with Bipolar Disorder and History of Sexual Trauma in Childhood

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Background: Bipolar disorder (BD) is associated with smaller corpus callosum (CC). Despite higher incidence of sexual trauma (ST) in childhood in females with BD, its effect on CC volume remains unknown.

Methods: Early Trauma Inventory Self Report – Short Form identified patients with history of ST in childhood (<18 years). We recruited 44 females in 3 groups: 1) Control with no history of ST (CNST, n = 18, Age 27.8 ± 2.2), 2) BD patients with no history of ST (BDNST, n = 12, Age 31.3 ± 2.7), 3) BD patients with history of ST (BDST, n = 14, Age 37.4 ± 2.9). The mean volumes of total and five sub-regions of CC were normalized to intracranial volume and compared across stated groups, after adjusting for age, education, IQ, age at diagnosis, and duration of illness.

Results: BDST group had significantly larger Anterior, Central, Posterior and total CC than BDNST [F (2, 29) = 4.51, p = 0.019; F (2, 29) = 3.36, p = 0.04; F (2, 29) = 3.74, p = 0.036, and F (2, 29) = 5.45, p = 0.009, respectively]. Mid-posterior CC was significantly larger in BDST group in comparison with CNST [F (2, 29) = 4.13, p = 0.026]. There were no difference in mid-anterior CC and cortical white matter volume between 3 groups.
Conclusions: Stress of sexual trauma in childhood, through neuroendocrine mechanisms and/or selective pruning, may differentially alter FC volumes in females with BD than females with BD but without ST.

Keywords: Neuroendocrine, Bipolar Disorder, Childhood Trauma, corpus callosum, cortical volume

615. Brain Volume Changes with Lamotrigine Treatment in Bipolar Type II Patients

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Background: Bipolar disorder (BD) is one of the major psychiatric disorder in clinical practice with a prevalence of 1-1.5% in general population. The treatment management of bipolar depression is a challenging area of clinical practice. Lamotrigine is typically used to treat depression and prevent relapse in BD patients. No study has, however, investigated the neural mechanisms underlying clinical improvement. This study compares the effects of lamotrigine on cortical and subcortical volumetric measures in depressive BD patients treated with lamotrigine.

Methods: Scans from 7 BD II patients and 12 age and gender-matched healthy controls were collected from the same Siemens 3T scanner at baseline and at 12-week follow-up BD patients were administered 100 mg of lamotrigine for 12 weeks. All the participants completed sociodemographic, clinical and side effect ratings scales. Imaging data was processed with FreeSurfer, and general linear models were used to detect longitudinal changes in a range of cortical and subcortical volumes.

Results: Full remission was achieved by 57% of BD patients. BD presented with increased volumes in the pars triangularis, 5th ventricle, and right frontal pole. BD Remitters had greater left putamen and caudate volumes than non-remitters. Remitters had smaller right caudate and left hemisphere pars triangularis whereas non-remitters had bigger right fusiform gyrus and 3rd ventricle than healthy controls.

Conclusions: These findings provide preliminary evidence of the link between treatment –response to lamotrigine in BD and basal ganglia, which are regions involved in reward-related impulsive behaviors. Given the well-established link between impulsivity and BD, future large-scale longitudinal studies are warranted to confirm these results, and determine whether basal ganglia may be a useful target for treatment of BD.

Keywords: bipolar II disorder, Subcortical Volume, Clinical-Trial, Neuroimaging, Free Surfer

616. Effects of Valproate on Brain Volumes in Pediatric Bipolar Disorder: A Preliminary Study

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Background: Sodium valproate (VPA) is known to be an effective treatment for pediatric bipolar disorder (PBD). Studies in animal models, and in adults with BD, have suggested neuroprotective effects of this medication. Less is known about VPA neuroprotective effect in PBD (PBD), and the structural brain changes caused by VPA in early ages. The present preliminary study aims to shed light on that matter.

Methods: Nine untreated PBD patients (Age: 13.63 ± 3.12 years) underwent a baseline clinical assessment including the Clinical Global Impression (CGI) scales, a structural MRI, and were enrolled in a 6-week trial of VPA. Six weeks later, all of them underwent the same evaluation. Brain volumes were corrected for intracranial volume, and analyzed using repeated measures ANCOVAs with CGI depression or mania as factor, and age and gender as covariates. Results were adjusted with Bonferroni correction.

Results: Results showed a significant CGI*Time interaction in the right precentral gyrus volume (p = 0.03), for CGI mania score, and in the right rostral anterior cingulate cortex (rACC ; p = 0.01) volume for CGI depression. Volumes in both regions decreased in non-remitters, but remained stable in remitters.

Conclusions: These preliminary findings suggest that, along with remission, VPA treatment may prevent brain alterations in PBD. The decrease of precentral and rACC volumes observed in non-remitters is consistent with PBD literature. These regions are involved in cognitive inhibition and emotional processes, which are typically impaired in BD. These findings need to be confirmed by large-scale, longitudinal studies.

Keywords: Pediatric Bipolar Disorder, Volumetric, neuroprotective, brain development, Emotional processing

617. Higher Depressive Symptoms Are Associated with Lower Activation in the Orbital Frontal Cortex when Anticipating Negative Stimuli in Individuals with PTSD

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Background: The high prevalence of post-traumatic stress disorder (PTSD) and depression comorbidity is well established, with comorbidity rates often reported between 30 and 50%. Both PTSD and depression have debilitating long-term cognitive effects, though the majority of research
Supports By: The Department of Defense

Keywords: PTSD, Depression, Orbitofrontal Cortex, fMRI, anticipation

618. Disruptions in Resting State Functional Connectivity in Euthymic Bipolar Patients with Insomnia Symptoms

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Background: Insomnia is prevalent in bipolar disorder (BP) even during periods of euthymic mood, and, in the general population, primary insomnia is associated with aberrant functional connectivity. We compared resting state brain activity between BP with and without insomnia, and secondarily to healthy individuals.

Methods: We studied 54 subjects: 15 euthymic BP with insomnia (BP-I), 12 with no reported insomnia (BP-nol), and 27 age-, gender- and education-matched healthy individuals. Clinical measures, including residual symptom severity and the Conner’s Adult ADHD Rating Scale (CAARS) self-report scores, were used. We examined alterations in functional connectivity of the default mode network (DMN) and the task-positive network (TPN) between the two BP groups.

Results: As a group, BP did not differ from healthy individuals on any measure of TPN or DMN connectivity. However, within the TPN, decreased intraparietal sulcus (IPS) and frontal eye field (FEF) connectivity was observed in BP-I compared to BP-nol. The ADHD Index T scores and inattention or memory problems T scores were significantly higher in BP-I than BP-nol, but symptoms of mania, depression and psychosis did not differ.

Conclusions: Insomnia is prevalent in bipolar disorder (BP) even during periods of euthymic mood, and, in the general population, primary insomnia is associated with aberrant functional connectivity. In BP-I, decreased intraparietal sulcus (IPS) and frontal eye field (FEF) connectivity was observed, which may be related to increased symptoms of depression and inattention.
enzyme Fatty Acid Amide Hydrolase (FAAH) (rs324420, C385A) has been associated with obesity and metabolic syndrome. Here we tested whether brain FAAH levels are low and peripheral endocannabinoid levels are elevated in overweight individuals.

**Methods:** Overweight healthy subjects with body mass index (BMI) >25 kg/m² (n = 10, range 25.1-32.9 kg/m²) and controls with normal BMI (<25 kg/m²; n = 20; n = 18.7-24.9 kg/m²), matched for age, gender and FAAH polymorphism status, completed a positron emission tomography scan with the FAAH probe, [11C]CURB. Blood was taken to measure peripheral endocannabinoids (anandamide and 2-AG).

**Results:** There was no significant difference in brain FAAH levels ([11C]CURB binding; F(1, 27) = 12.76; p = 0.7) or in plasma endocannabinoid levels (p > 0.5) between healthy-weight vs overweight individuals. Regional FAAH was also not reduced in the 2 subjects with BMI >29.9 kg/m². BMI did not correlate with brain FAAH levels (all p > 0.5) but showed a trend relationship with plasma 2-AG (p = 0.089).

**Conclusions:** These preliminary results suggest that FAAH brain levels are not reduced in overweight individuals; however, these data need to be replicated in a larger sample. Additional measures such as adiposity indices and metabolic markers may provide more direct correlates of brain FAAH levels.

**Supported By:** NIAAA R21 AA022246-01A1; NIDA R21 DA036024

**Keywords:** Endocannabinoids, Positron Emission Tomography, BMI, Obesity, Fatty Acid Amide Hydrolase

**620. Cortical Networks Hyper- And Hypoconnectivity with Subcortical Nuclei is Specific and Links Distinctively with Cognitive and Psychotic Symptoms in Schizophrenia**

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**Background:** Schizophrenia is characterized by aberrant thalamo-cortical intrinsic functional connectivity (IFC), with decreases to limbic-cortical and increases to central-sensorimotor areas. However, previous studies of thalamic IFC were mostly restricted to anatomically defined corticobase nuclei neglecting functional cortex organization. The current study hypothesized that thalamo-cortical hypo- and hyperconnectivity extends to cortical intrinsic brain networks (IBNs), which estimate functional cortex organization and are based on cortical IFC. Furthermore, we explored whether subcortical-cortical hypo/ hyperconnectivity is associated with symptom dimensions.

**Methods:** Resting-state MRI data of 71 patients with schizophrenia and 72 healthy controls were decomposed with independent component analysis, and 7 cortical IBNs were selected due canonical cortex IFC-parcellation. Based on partial correlations with these IBNs, we segmented thalamus as well as striatum and pallidum by assigning voxel membership to each IBN, respectively. This procedure resulted in correlation maps, on which subsequent voxel-wise two-sample t-tests were calculated. Averaged z-values of clusters depicting group differences were then partially correlated with scores of cognitive impairment and psychotic symptoms.

**Results:** Concerning thalamus, we found specific hypoconnectivity between salience network (SAL) and ventral posterolateral nuclei as well as hyperconnectivity between auditory-sensorimotor network (A-SM) and ventral anterior nuclei in patients. SAL-thalamic hypoconnectivity was specifically associated with cognitive impairment, while A-SM-thalamic hyperconnectivity correlated with positive symptoms. We controlled for age, gender, IQ, and medication. Similar dysconnectivity patterns and associated symptom dimensions were found for both striatum and pallidum.

**Conclusions:** Results demonstrate intrinsic brain network-specific subcortical-cortical hypo- and hyperconnectivity in schizophrenia, with distinct links to symptom dimensions.

**Keywords:** Resting state fMRI, Schizophrenia, Dysconnectivity, Subcortical Structures, Brain networks

**621. Risk Profile Score (RPS) and Prefrontal Cortical Activation in Patients with Schizophrenia during Working Memory**

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**Background:** Prior reports have investigated the relationship between schizophrenia-based risk RPS and disease-related phenotypes. One phenotype, prefrontal activation during working memory tasks, has been shown to be both heritable and associated with RPS. Here, we sought to characterize the relationship between RPS and prefrontal functioning in patients with schizophrenia during a working memory task.

**Methods:** GWAS SNP data and BOLD fMRI were collected on 150 patients with schizophrenia while performing the N-back task. RPS was calculated at fourteen different thresholds from Pthreshold = 1x10-8 to 1 using the PGC schizophrenia results. After extracting mean 2-back activation values from bilateral DLPFC (BA 10) ROIs, fourteen multiple regressions were performed to examine the relationship between RPS and prefrontal working memory-related activity, controlling for age, sex, performance, and principle components measuring population stratification.

**Results:** In patients, RPS from the most permissive SNP thresholds (pthreshold = 0.3-1) predicted brain activation of left DLPFC (BA10), such that with increasing polygenic risk, greater working memory-related activation was seen (r² = 0.03, p-value = 0.04). At more stringent SNP thresholds, RPS wasn't associated with working memory activation. However, none of these values survive multiple correction.

**Conclusions:** At trend level, our data suggest that RPS is associated with left BA10 activation and the relationship was strongest at the more permissive RPS thresholds from Pthreshold = 0.3 to 1. This supports the notion of a complex polygenic pathophysiologic mechanism in schizophrenia, as RPSs capture more variance when using a greater number of less significant SNPs, similar to prior findings with other disease-related phenotypes.

**Supported By:** NIMH
Keywords: Polygenic Risk, Schizophrenia, BOLD fMRI, GWAS, Dorsolateral Prefrontal Cortex

622. Neural Correlates of Self-Reflection in Schizophrenia: A Functional Magnetic Resonance Imaging Study

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National Institute of Mental Health and Neurosciences

Background: Self-reflection is the process of conscious evaluation of one’s traits, abilities and attitudes. Deficient self-reflective processes might underlie lack of insight in schizophrenia. The limited literature on neural correlates of self-reflection in schizophrenia is inconclusive. In this study, we investigated the neural correlates of self-reflection in schizophrenia patients attending a tertiary care hospital in India.

Methods: 19 male schizophrenia patients and 19 healthy controls participated in the study. Participants performed self-reflection task while undergoing fMRI. The task comprised of 4 domains: Self-reflection, Other-reflection, Affect labelling and Perceptual. Contrasts comparing Self-reflection with other domains were modelled at the individual subject level. In second level, independent t test was used to compare 2 groups. The results were thresholded at p<0.001 (uncorrected, cluster size 6 voxels).

Results: For Self-reflection > Other-reflection contrast, patients demonstrated greater activation of both superior parietal lobules (BA 5,7), right inferior parietal lobule (BA 39), left parahippocampal gyrus (BA 36) and left premotor cortex (BA 6). For Self-reflection > Affect labelling contrast, patients showed greater activation of precuneus (BA 7) and right inferior occipital gyrus (BA 19), lesser activation of left inferior frontal gyrus (BA 45,47). For Self-reflection > Perceptual contrast, patients showed greater activation of left middle frontal gyrus (BA 10), left posterior cingulate gyrus (BA 31), right superior parietal lobule (BA 7), both inferior parietal lobules (BA 39,40) and left premotor cortex (BA6).

Conclusions: The results indicate that patients have aberrant activity in brain regions subserving self-reflection. The greater activation of posterior brain areas might suggest that schizophrenia is associated with an anterior-to-posterior shift in introspection-related activation, as seen from earlier studies. Further studies with a larger sample are needed to examine neural processes underlying self-reflection abnormalities in schizophrenia.

Supported By: Department of Science and Technology, Govt. of India - INSPIRE Faculty Award (IFA12-LSBM)

Keywords: Self-reflection, Schizophrenia, fMRI, Insight

623. Classification of First-Episode Schizophrenia Spectrum Disorders and Controls from Whole Brain White Matter Fractional Anisotropy Using Machine Learning

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Background: Early diagnosis of schizophrenia could improve the prognosis of the illness. Applying machine learning (ML) to MRI data allows for identification of subtle disease patterns on a single subject level, which could help realize the diagnostic potential of MRI in psychiatry. Machine learning has mostly been tested for diagnostic purposes in combination with gray-matter structural or functional MRI. Here, we used ML to differentiate participants with a first episode of schizophrenia-spectrum disorder (FES) from healthy controls based on diffusion tensor imaging data.

Methods: We attempted a diagnostic classification of 77 FES patients and 77 age and sex matched healthy controls, by applying linear support-vector machine (SVM) to fractional anisotropy data. We further analyzed the effect of medication and symptoms on the classification performance using standard statistical measures (t-test, linear regression) and machine learning (kernels, ridge regression).

Results: The SVM distinguished between patients and controls with significant accuracy of 62.34 % (p=0.005). There was no association between the classification performance and medication nor symptoms.

Conclusions: This is a proof of concept that SVM in combination with brain white-matter fractional anisotropy might help differentiate FES from HC, even early in the course of schizophrenia. The classification was probably based on trait rather than state markers, as symptoms or medications were not significantly associated with classification accuracy.

Supported By: Nr. LO1611 with a financial support from the MEYS under the NPU I program.

Keywords: first episode schizophrenia, Machine learning, Fractional Anisotropy, Diffusion Tensor Imaging (DTI), Support Vector Machines

624. Accelerated Brain Ageing in First Episode Psychosis. Association with Metabolic Parameters

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Accelerated brain ageing. Confidently contributing to brain alterations in psychosis.

Methods: To investigate whether metabolic changes contribute to brain alterations in psychosis, we obtained metabolic and structural MRI data from 157 patients hospitalized for first episode of psychosis (FEP) and 115 healthy controls. To evaluate structural integrity of the brain, we estimated biological age of the brain by applying machine learning kernel regression methods to MRI anatomical data. We calculated BrainAge scores by subtracting chronological age from the calculated brain age.

Results: Participants with FEP had a higher BrainAge score than controls (t(270)= 3.91; p<0.001). The brain age of FEP subjects was 1.56±4.5 years greater than their chronological age (t(156)=4.37, p<0.001). Across all subjects, higher BrainAGE scores were positively correlated with body mass index (r=0.14, p=0.028), particularly weight (r=0.18, p=0.005) and negatively correlated with HDL (r=-0.19; p=0.012).

Conclusions: Already young participants at the early stages of psychosis showed accelerated brain ageing, with an average difference between brain and chronological age of 1.55 years. Weight and HDL significantly contributed to accelerated brain ageing. Confirming that obesity and dyslipidemia are risk factors for brain changes in FEP could be the first step toward the prevention or treatment of accelerated brain ageing in psychosis.

Supported By: Agency for the Czech Republic health research (grant number 16-32791A); DFG (German Research Foundation; FR 3709/1-1)

Keywords: First episode psychosis (FEP), brain aging, modifiable risk factors, magnetic resonance imaging (MRI), obesity

625. Analysis of Glutamate Levels Measured with Magnetic Resonance Spectroscopy (MRS) in the Anterior Cingulate Cortex (ACC) of Patients with Schizophrenia, Unaffected Siblings, and Healthy Volunteers

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Background: Abnormalities in glutamatergic transmission have been implicated in schizophrenia and several studies have found altered glutamatergic neurometabolites using MRS, although many could not clearly separate glutamate from glutamine. We obtained measures specific for glutamate in a large sample of treated (SCZ) and untreated (SCZ-UTR) patients with schizophrenia, their unaffected siblings (SIB) and healthy volunteers (HV).

Methods: 228 HV, (59% F, age 31.2±9.6 SD), 95 SCZ, (33% F, age 30.4±8.7), 32 SCZ-UTR (34% F, age 28.4±9.7), and 36 SIB (36% F, age 30.3±10.8) were scanned with MRS (TE-averaging sequence on a 3T scanner, 18 cc dorsal ACC voxel). Levels of N-acetyl aspartate (NAA), choline (Cho), and glutamate (Glu) were expressed as ratios to creatine. Backward stepwise multiple regression models were used to compare neurometabolite measures across groups.

Results: There was a significant effect of group for all metabolite ratios, due to differences between SCZ and HVs (p<9*10^-6, for all metabolites) and SCZ and SIBs (p<8*10^-3, for all metabolites), while SCZ-UTR did not differ from any other group.

Conclusions: These data do not support familial risk for glutamate measures with this MRS acquisition. It is possible that medication effects, either on metabolite concentrations or on their T2, may be responsible for these findings. We are pursuing further data analysis to improve data interpretation.

Supported By: NIMH

Keywords: Schizophrenia, MRS

626. Reward Learning and Dopamine Release in Adults with 22q11DS: A Study Using [18F]fallypride Positron Emission Tomography

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Background: 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with an increased risk for psychosis. A dysfunctional motivational reward system is thought to be one of the salient features in psychosis caused by abnormal dopamine functioning. It is unknown whether patients with 22q11DS have a dysfunctional reward system.

Methods: We included 12 adults with 22q11DS (age: 34.6 years, 67% females) and 16 healthy controls (HC, age:38.1 years, 75% females). A single infusion DA D2/3 receptor [18F] fallypride positron emission tomography (PET) scan was acquired to investigate the DAergic activity in striatal (putamen, caudate nucleus, ventral striatum) and frontal regions. During the PET scan all subjects performed a version of the learning phase of the Probabilistic Stimulus Selection Task for reward learning (RL), modified to deliver social feedback.
Results: IQ-scores were significantly lower in the 22q11DS group (p<.001) compared to HC. The 22q11DS group earned significantly less money (p <.05) and performed worse during the RL-task (p <.05) than HC. The preliminary PET analyses show that the percentage of active voxels during reward learning is significantly higher in 22q11DS compared to HC in the right caudate nucleus (p <.05).

Conclusions: These results indicate that people with 22q11DS are less susceptible for reward than HC because their overall performance during RL is worse than HC. In addition, people with 22q11DS showed different special extent of reward-induced DA release in striatal regions compared to HC. The lower reward sensitivity could be a result of haplo-insufficiency of COMT in 22q11DS and consequently abnormal dopamine functioning.

Keywords: 22q11 Deletion Syndrome, PET imaging, Reward Learning


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Background: Schizophrenia (SZ) and autism spectrum disorders (ASD) share phenotypic similarities and genetic risk factors and have been reported to co-occur at elevated rates, stimulating debate about shared underlying neuropathology. The current study examined fMRI functional connectivity in SZ, ASD and healthy controls (HC), within the default mode network (DMN).

Methods: Resting-state fMRI was collected from 100 individuals: 33 SZ, 33 ASD, 34 HC (ages 18-35). Temporally distinct resting state components were determined using the group independent component analysis (ICA) toolbox (GIFT) with a 100 components model. Eight components were identified as DMN nodes, based on the Stanford functional ROI atlas [http://findlab.stanford.edu/functional_ROIs.html], including 2 frontal, 4 posterior cingulate (PCC), one precuneus (PrC) and one lateral parietal (LP) nodes. The functional network connectivity (FNC) toolbox was used to compute group differences in DMN components coherence (i.e. connectivity, measured as between nodes correlations).

Results: One way ANOVA demonstrated significant group effect for four pairs of DMN nodes. Post-hoc pair-wise group comparisons indicated that in three of those node-pairs (PCC1-PCC2 p = .006; PCC1-PrC p = .024; PCC2-PrC p < .001) both SZ and ASD had significantly lower correlation than HC (with SZ and ASD not significantly different from each other). For the fourth node-pair (PrC-LP p = .025), SZ showed significantly lower correlation than HC (and although not significant, ASD showed a similar pattern).

Conclusions: These preliminary results indicate lower intra-DMN functional connectivity in both SZ and ASD groups, as compared to HC. Interestingly, connectivity of the PCC and PrC (main posterior DMN hubs), was mainly implicated.

Keywords: Schizophrenia, ASD, Functional connectivity, Default Mode Network, Resting state fMRI

628. Polygenic Risk Score for Schizophrenia of CREB1 and BDNF Associated with Structural Brain Dysconnectivity

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Background: Since genetic variations influence both schizophrenia (SZ) and brain structure, investigating shared genetic risk between neurobiological and clinical traits may help bridge the gap between genome and phenotype. Here, we examined brain structural dysconnectivity for the association with CREB1 and BDNF, the only two genes suggested as involved in white matter development by Gene Ontology among those hosting SZ-discriminating SNPs (p<1E-04) in the Psychiatric Genomic Consortium study.

Methods: We calculated the polygenic risk score (PRS) of 27 SNPs mapped to CREB1 and BDNF in 244 SZ patients and 290
healthy controls. We then computed whole-brain deterministic tractography analysis from diffusion imaging, and conducted the connectivity analysis (number of streamlines) among 70 cortical regions of the Desikan-Killiany atlas. The white matter connectivity (WMC) was thresholded at 10, resulting in 341 features which were decomposed by independent component analysis into 13 components capturing clusters of WMC covarying across subjects. An ANOVA test was used to identify SZ-discriminating WMC components, which were evaluated for associations with the PRS.

**Results:** Four WMC components showed group differences, one of which significantly correlated with PRS after controlling for age, sex, site and diagnosis (r = -0.12, p = 6.44E-03, passing Bonferroni correction). The associated component presented significantly higher WMC in controls than patients between three pairs of regions (p = 9.32E-07): 1) bilateral orbitofrontal and rostral-middle-frontal cortices, 2) bilateral pars-triangularis and rostral-middle-frontal cortex, 3) right insula and right orbitofrontal cortex.

**Conclusions:** Our findings suggest that CREB1 and BDNF may influence schizophrenia risk by mediating regional structural connectivity.

**Supported By:** National Institutes of Health grants P20GM103472

**Keywords:** Schizophrenia, CREB, BDNF, structural connectivity, polygenic risk score

629. Dynamic Network Reorganization of the Frontal-Parietal, Aalience, and Default Mode Networks during Cognitive Control and Episodic Memory

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**Background:** We explored dynamic integration and segregation of functional brain networks in healthy controls (HC) performing fMRI tasks varying in cognitive control (CC) demands. We used a novel graph theory approach that leverages opposing network structure to highlight dynamic reorganization. We hypothesized that the frontal-parietal network (FPN) uniquely integrates with other higher-cognitive networks, manifesting as differential modular organizations across task conditions.

**Methods:** 52 HCs performed two fMRI tasks: the RISE (an episodic-memory task that manipulates CC demands via context dependent encoding and retrieval) and DPX (a task that engages proactive CC via a sequence of cue-probe stimuli where cues indicate the need for high (B-cue) or low (A-cue) CC). Beta-series regression captured trial specific BOLD effects for each condition. Beta-series pairwise correlations for 245 nodes were extracted to obtain modular partitions of each task condition. Changes in compositions across tasks were quantified using mutual information(M).

**Results:** Containing 7-9 modules across tasks, all functional partitions were more modular than the null (F(1,51) = 2497, p < 0.001). Modules were most similar between A- and B-cues (M = 0.928) in the DPX, with less agreement between RISE encoding (M = 0.888) and retrieval conditions (M = 0.823). FPN integration/segregation varied across tasks, uniquely integrating with DMN and salience networks in multiple modules across RISE conditions, but segregated into one module in DPX conditions.

**Conclusions:** The FPN shows a unique capacity to flexibly support CC via dynamic network integration/segregation. FPN segregation supports proactive CC during the DPX, while complex FPN integration supports RISE encoding and retrieval. FPN inflexibility may underlie CC impairments in schizophrenia patients. Data will be presented contrasting current results to that seen in schizophrenia.

**Supported By:** NIMH-5R01MH1059883

**Keywords:** BOLD fMRI, graph theory, Cognitive Control Network, Functional connectivity, network connectivity

630. Free Water Alterations in the First Episode Psychosis: A 12-Month Longitudinal Study

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**Background:** Recent findings from clinical epidemiology and developmental neurobiology have led to the hypothesis that altered signallng of immune molecules in the brain may underlie altered brain connectivity in psychosis. These ideas have received support from studies of peripheral cytokines, PET data, and postmortem tissue, where findings have suggested the presence of neuroinflammation in individuals with schizophrenia and severe mood disorders. New developments in diffusion weighted imaging have suggested indexes of free water, a putative marker of neuroinflammation, are elevated in patients with psychosis. In the present study, we sought to confirm the presence of increased brain free water in first episode psychosis (FEP) and to determine if and how this may change over the first year of the illness.

**Methods:** 83 schizophrenias, 35 bipolar patients and 70 healthy controls were recruited at baseline, where 64 of them returned for the follow-up study after 12 months of treatment. We estimated free water in GM and WM using FSL and free water elimination software.

**Results:** FEP showed significantly increased free water in GM at baseline, mainly driven by bipolar patients. Repeated measures ANOVA revealed no change in free water over time.

**Conclusions:** Our results support the presence of GM inflammation in FEP, and suggest that this finding remains stable during the early course of the illness, with no evidence of either progression or remission.

**Keywords:** Diffusion Tensor Imaging (DTI), Extracellular Free Water, First-Episode Psychosis (FEP), immunoinflammation


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Background: Since Emil Kraepelin’s conceptualization of endogenous psychoses as dementia praecox and manic depression the separation between primary psychotic disorders and primary affective disorders has been much debated.

Methods: We conducted a systematic review of case-control studies contrasting magnetic resonance imaging studies in schizophrenia and bipolar disorder. A literature search in PubMed of studies published between January 2005 and December 2016 was conducted.

Results: 50 structural, 29 functional, 7 magnetic resonance spectroscopy, and 8 combined imaging and genetic studies were deemed eligible for systematic review. Structural neuroimaging studies suggest white matter integrity deficits that are consistent across the psychosis spectrum, while gray matter reductions appear more widespread in schizophrenia compared to bipolar disorder. Spectroscopy studies in cortical gray matter report evidence of decreased neuronal integrity in both disorders. Functional neuroimaging studies typically report similar functional architecture of brain networks in healthy controls and patients across the psychosis spectrum, but find differential extent of alterations in task related activation and resting state connectivity between illnesses. The very limited imaging-genetic literature suggests a relationship between psychosis risk genes and brain structure, and possible gene by diagnosis interaction effects on functional imaging markers.

Conclusions: While the existing literature suggests some shared and some distinct neural markers in across schizophrenia and bipolar disorder, it will be imperative to conduct large, well designed, multi-modal neuroimaging studies in medication-naïve first episode patients that will be followed longitudinally over the course of their illness in an effort to advance our understanding of disease mechanisms.

Supported By: National Institute of Mental Health (R01MH102951, ACL; K23MH106683, NVK).

Keywords: Schizophrenia, Schizoaffective disorder, Bipolar disorder, Magnetic resonance spectroscopy, Functional magnetic resonance imaging, Diffusion tensor imaging, gray matter, white matter, resting state

632. Combining Neuro-Imaging and Non-Invasive Brain Stimulation for Clinical Intervention in Alcohol Use Disorder

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Background: New interventions are needed to improve high relapse rates in alcohol use disorder (AUD). We have neuroimaging evidence showing that individuals with AUD with long-term abstinence have higher resting functional connectivity (FC) in a network including prefrontal cortex, thalamus and nucleus accumbens than those with short-term abstinence. Low FC in this network during early abstinence predicts subsequent relapse. Literature shows that thalamus-prefrontal FC can be enhanced with transcranial direct current stimulation (tDCS).

Methods: We investigated whether thalamus-prefrontal FC can be enhanced in AUD with a double-blind longitudinal study design. Intervention: 10 cognitive training sessions combined with either sham-tDCS or active-tDCS (anode on left dorsolateral prefrontal cortex). Rest fMRI data was collected pre- and post-intervention. Two AUD subjects undergoing active tDCS were compared to two AUD subjects undergoing sham tDCS. Preprocessing used FSL-FEAT and Melodic-ICA denoising. We hypothesized that individuals assigned to receive stimulation on left dorsolateral prefrontal cortex would show increases in thalamus-prefrontal FC when compared to individuals assigned to receive sham-tDCS.

Results: Preliminary analyses examining FC between left thalamus and left dorsolateral prefrontal cortex showed that subjects assigned to active-tDCS had a significant within-group FC increase (t=20.87, p=0.037) while subjects assigned to sham-tDCS did not (t=0.27, p=0.832). Group x Time effects was eta-square $\eta^2 = 0.116$

Conclusions: These pilot data suggest tDCS can improve thalamic-cortical connectivity. Larger sample size and treatment outcome information will provide crucial evidence supporting the therapeutic use of interventions targeting both cognitive and underlying neural mechanisms that support abstinence.

Supported By: CTSI (Clinical and Translational Science Institute)

Keywords: Alcohol Use Disorder, Neuromodulation, Neuroimaging, Functional connectivity, intervention

633. The Self and Susceptibility: The Role of the Medial Prefrontal Cortex in Addiction Comorbidity

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Background: Individuals with drug use disorders (DUD) co-occurring with other psychiatric disorders have poorer treatment outcomes than individuals without co-occurring disorders. Based upon prior research relating medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) function and structure with resilience against and susceptibility to DUD and other forms of psychopathology, we hypothesized that these regions would also be associated with the degree of susceptibility for childhood trauma-exposed men and women to develop comorbid DUD.

Methods: A sample of adults with childhood maltreatment (n=79) was divided into the following groups based on DSM-IV psychiatric diagnoses and drug use history: no current or past psychiatric disorders (resilient, used as a trauma control sample), DUD only, MDD/PTSD only, and comorbid DUD with MDD/PTSD. Using a 200-node functional brain atlas, robust regression identified differences in ACC and/or DLPFC resting-state functional connectivity (FC) between groups. These group-level FC differences were then related to individual differences in psychiatric symptomatology, trauma history, and self-schema using Spearman’s correlation followed by elastic net regression. Bootstrapped mediation analyses were then performed on the comorbid and DUD subgroups to further explore the relationship between trauma, FC, and negative self-schema.

Results: Increased VMPFC–hippocampal FC was found to mediate the relationship between physical neglect and...
negative self-schema traits (Pessimism, Self-Criticism, and Indecisiveness) in the comorbid subgroup.

**Conclusions:** Our findings suggest that comorbidity is not a simple conglomeration of DUD and other psychopathology, but involves unique neural processing in MPFC networks related to self-representation that are altered by childhood trauma.

**Supported By:** T32DA022981

**Keywords:** Addiction, Resting state fMRI, Comorbidity, Childhood Trauma, Resilience

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**Background:** Cocaine addiction is associated with dysfunction of the dopaminergic reward circuit and reinforcement learning. However, it is unknown if cocaine users can actively self-regulate neural activity or even learn to improve self-regulation capabilities in the substantia nigra/ventral tegmental area complex (SN/VTA). Real-time fMRI (rtfMRI) neurofeedback training (NFBT) is a promising method enhancing the ability to self-regulate neural activity with positive mental imagery in the dopaminergic reward system. For the first time, we tested this non-invasive cognitive neurostimulation method in cocaine users (CU) to evaluate its potential as novel treatment approach.

**Methods:** 24 CUs 29 healthy controls (HC) performed a rtfMRI block design task in sessions with or without visual feedback of neural activity in the SN/VTA. In the active condition, we instructed participants to voluntarily up-regulate the activity in SN/VTA by recalling non-drug related rewarding scenes. In the neutral condition no active imagery was performed.

**Results:** Both groups were able to self-activate SN/VTA activity and other reward coding regions e.g. hippocampus, nucleus accumbens and orbitofrontal cortex (FWE corrected p < 0.05). Furthermore, both groups improved this self-regulation ability with rtfMRI NFBT (F = 6.74, p < 0.01), but no effect of group was observed (F = 0.22, p < 0.639536).

**Conclusions:** Cocaine users are able to actively self-regulate neural activity in the dopaminergic reward system and to improve this ability with rtfMRI NFBT. To elucidate the potential of rtfMRI NFBT as non-invasive treatment strategy future research should focus on the impact of cognitive neurostimulation with neurofeedback on clinical outcome in cocaine addiction.

**Supported By:** Hartmann Mueller Foundation Zurich

**Keywords:** real-time fMRI neurofeedback, Dopaminergic circuitry, cocaine addiction, functional imaging, Reward Learning

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**635. The Influence of Intelligence, Cortical Thickness, Surface Area, and White Matter Connectivity on Child Sexual Abuse Behavior by Pedophiles**


**Background:** Pedophilia is a heterogeneous disorder for which the neurobiological correlates are not well established. In particular, there are no biological markers identifying individuals with high risk to commit sexual abuse of children.

**Methods:** Pedophiles who have committed child sexual offense (P+CSO; N=73), pedophiles who have not committed child sexual offense (P-CSO; N=77), and healthy controls (HC; N=133) were assessed via full scale IQ performance, and multimodal structural neuroimaging measures including: cortical thickness (CT), surface area (SA), and white matter fractional anisotropy (FA), and on IQ performance. Cortex-wise mediation analysis used to assess the relationships among brain structure, IQ and child sexual abuse behavior.

**Results:** Lower IQ performance was strongly associated with P+CSO (P+CSO vs P-CSO: χ² = 16.1, P = 6.0x10^-6; P+CSO vs HC: χ² = 10.7, P = 0.0011), P+CSO had lower CT in the right motor cortex (PFWE-corrected < 0.05), had strong reductions in SA spanning the bilateral frontal, temporal, cingulate, and insula regions (PFWE-corrected < 0.05). P+CSO had lower FA particularly in the corpus callosum (PFWE-corrected < 0.05). The relationship between SA and P+CSO was significantly mediated by IQ with particularly in the prefrontal and anterior insular cortices (PFWE-corrected < 0.05).

**Conclusions:** This study demonstrates that, among pedophiles, converging neurobiological findings in P+CSO including lower IQ performance, cortical thickness, surface area, and FA with near identical neuroanatomical differences between P+CSO and HC. Further, IQ potentially mediates abuse by pedophiles via aberrant SA, whereas the CT and FA associations were independent of IQ differences. These findings suggest aberrant neuroanatomy and lower intelligence as a potential core feature underlying child sexual abuse behavior by pedophiles.

**Supported By:** CIHR, BMBF

**Keywords:** Pedophilia, Cortical Thickness, Cortical surface area, Diffusion Tensor Imaging (DTI), Mediation Analysis
636. Combining Transcranial Direct Current Stimulation with Virtual Reality Exposure for PTSD

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**Background:** Exposure-based therapy for posttraumatic stress disorder (PTSD) uses tenets of extinction to reduce symptoms – a process supported by the ventromedial prefrontal cortex (vmPFC). Although efficacious, many Veterans with PTSD suffer from continued symptoms after treatment. Facilitating endogenous vmPFC activity using non-invasive brain stimulation may improve extinction-related processes to ultimately improve exposure-based treatments. To this end we are exploring whether transcranial direct current stimulation (tDCS) augments habituation of repeated presentation to standardized warzone-related virtual reality scenes in Veterans with PTSD.

**Methods:** Nine Veterans with PTSD completed six virtual reality exposure sessions while receiving either 25 minutes of 2 mA anodal tDCS or sham stimulation over AF3, intended to target vmPFC. Primary outcome measures were psychophysiological arousal during each virtual reality session and pre-post assessment of self-report PTSD symptom severity.

**Results:** Preliminary data demonstrate clinically meaningful reductions in PTSD symptom severity (pre: 46.50 ± 13.5; immediate post: 32.67 ± 15.4; one-month follow-up: 29.33 ± 14.91; p = .02) on the PTSD checklist, and psychophysiological arousal (session 1: .94 ± .97 μS; session 6: .42 ± .69 μS; p = .047). All participants reported tDCS to be tolerable and could not accurately guess which treatment they received (p = .49). One participant reported headaches after tDCS session six, five participants reported mild scalp uncomforableness or scalp sensations, and two participants reported an acute mood change after the first tDCS session only.

**Conclusions:** These results provide technical feasibility and preliminary findings on combining tDCS with exposure-based processes to further test the potential of this protocol to improve psychophysiological habituation and PTSD-related symptomatology.

**Supported By:** VA RR&D, Center for Neurorestoration and Neurotechnology

**Keywords:** PTSD - Posttraumatic Stress Disorder, Exposure Therapy, Extinction, Treatment, noninvasive brain stimulation

637. Aggression, Expressed Emotion and Re-Admissions in Pediatric Inpatients: A Common Pathway?

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**Background:** Aggression is not only a common problem in youth with mental illness but it is a strong predictor for hospitalization. Elevated family stress as measured by expressed emotion (EE) in primary caretakers has been associated with increased relapse in patients with mental illness. The current study examined aggression in pediatric patients admitted to an acute psychiatric facility and its relationship with primary caretaker EE.

**Methods:** 87 caretakers of patients aged 8-17 (mean ± SD yr., 14.04 ± 0.28) admitted to an inpatient unit were interviewed within 5 days of admission. The standardized interview consisted of the Five Minute Speech Sample (FMSS), a measure of EE, which was subsequently coded utilizing the EE and FMSS coding systems. Caregivers also completed the Modified Overt Aggression Scale (MOAS) that measures four aggression types: verbal, physical, object and self-directed. Total and subscale MOAS scores were compared to EE ratings (High/Low) using independent sample t-tests. Linear regression was used to examine relationship between total MOAS score and clinical variables (length of stay, number of hospitalizations).

**Results:** 56/87 (64.4%) caregivers were classified as having high EE. The total and verbal, physical and object aggression subscales were significantly higher in High EE caregivers (p <.05). Total MOAS scores had positive linear association with number of hospitalization (R2 = 0.207).

**Conclusions:** Re-hospitalization is common in pediatric mental illness and leads to increased healthcare costs. These results suggest aggressive behavior in children is associated with high EE in caretakers and may increase hospitalizations.

**Supported By:** APA Resident Research Psychiatric Scholars Fellowship 2015 awarded to Isha Jalnapurkar

**Keywords:** children and adolescence, Expressed Emotion

638. A Novel fNIRS-Based Neurocognitive Intervention for Targeted Enhancement of Executive Function Network in ADHD

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**Background:** Executive function (EF) deficit is associated with a host of serious brain disorders including ADHD, depression and autism. Current treatments for EF deficits do not account for differences in brain networks across multiple disorders and thus lack specificity. We propose a novel intervention that is based upon rehabilitation of individualized neural systems underlying EF.

**Methods:** The proposed intervention is the first that combines real-time functional near-infrared spectroscopy (fNIRS) and multivariate pattern analysis, in conjunction with computerized cognitive rehabilitation for targeted enhancement of EF network. Here, we discuss the innovative aspects of the proposed approach along with the preliminary results of validating this technique in children with ADHD.

**Results:** We argue that the proposed approach expands current cognitive intervention techniques in two ways: (1) The proposed intervention integrates real-time fNIRS imaging and computational
639. Effect of rTMS on Resting-State Functional Connectivity in Patients with Major Depression

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Background: Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved treatment for major depression, but its mechanism of action remains unclear. Patients with depression show abnormalities in resting-state functional connectivity. We hypothesize that rTMS may exert its effects by normalizing connectivity patterns, particularly from frontal executive control regions where stimulation is often directed.

Methods: Forty-four patients (35.2±8.8 years, 27 females) with recurrent major depressive disorder entered a sham-controlled, double-blinded, randomized trial of 10-Hz rTMS to the left dorsolateral prefrontal cortex (dIPFC), corresponding to a neuronavigated target lying within the fronto-parietal executive network. fMRI scans at baseline and after 20 rTMS sessions were obtained during rest, and global functional connectivity was calculated between the stimulation site and the rest of the brain (root-mean-square of correlation coefficients). Clinical response was quantified with the Hamilton Depression Scale (HamD-24). Results were compared to 28 healthy volunteers (34.5±10.6 years, 15 females) who underwent scanning without rTMS.

Results: Compared to controls, patients exhibited reduced global connectivity from left dIPFC (p<0.05 FDR-corrected). Connectivity did not change after receiving active rTMS versus sham across all patients. However, patients whose symptoms improved after rTMS showed increased connectivity after treatment (p<0.05 FDR-corrected), driven in part by stronger negative connectivity between left dIPFC and left amygdala (p<0.05 FDR-corrected). Reduced global connectivity at baseline predicted treatment response (p<0.05 FDR-corrected).

Conclusions: Our results demonstrate that rTMS modulates functional connectivity networks, normalizing global patterns of connectivity between the stimulation target and the rest of the brain, only in patients who benefited from treatment.

Supported By: Dana Foundation
Keywords: rTMS, Major Depression, Functional connectivity, Resting state fMRI, Dorsolateral Prefrontal Cortex

640. Lipidomics in Patients Receiving ECT

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Background: There is evidence for an altered lipid metabolism in major depressive disorder (MDD). Electroconvulsive therapy (ECT) is the most effective acute treatment of MDD. The mechanisms of action of ECT are unknown, but might include changes in lipid metabolism. The aim of the study was to assess changes in serum lipid concentrations as part of a multidisciplinary trial investigating the mechanisms of ECT.

Methods: Serum lipid levels were measured in 16 treatment resistant MDD patients using a non-targeted lipidomics approach. Blood samples were obtained before first treatment and one week after the treatment series. Ultrahigh performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) technology was used to detect lipid metabolites. A matched pairs t-test was used to compare pre and post-treatment samples.

Results: 399 lipid metabolites were investigated, of which 69 were significantly altered after ECT. Post-treatment samples showed reduction of serum concentration in several classes of lipid metabolites, especially free fatty acids (FFA). Significant decreases were found in nearly all of the detected monoacylglycerol species, within several diacylglycerol species, several lysolipids and other phospholipid breakdown products and a number of fatty acid dicarboxylates.

Conclusions: The observed changes in lipid levels can be mediated by several processes, including changes in biosynthesis and breakdown rates of FFAs. More investigations are needed to explore the nature of these processes. The study contributes to elucidate the role of lipid metabolism in MDD and the effects of ECT. Further investigations in larger samples should be performed to confirm these results and evaluate the clinical significance of the findings.

Supported By: KG Jebsen Center for Neuropsychiatric Disorders; Western Norway Regional Health Authority
Keywords: Electroconvulsive therapy (ECT), Major Depressive Disorder (MDD), Metabolomics, lipids, Treatment Resistant Depression
641. Neurocognitive Predictors of Antidepressant Efficacy to Transcranial Direct Current Stimulation: Results from an International Randomized Controlled Trial

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Background: Transcranial direct current stimulation (tDCS) has shown variable efficacy, however, clinical trials have shown variable efficacy. Pre-treatment executive functioning has been identified as an inter-individual predictor of efficacy. In this study we investigated clinical and neurocognitive predictors from a large multicenter clinical trial.

Methods: The study was a triple-masked, parallel, randomized, controlled design across 6 international academic medical centers. Participants were randomized to active (2.5mA for 30 minutes) or sham (34µA, and two 60-second current ramp-ups of 1 and 0.5milliamperes) tDCS for 20 sessions. The anode was centered over the left dorsolateral prefrontal cortex at F3 (10/20 EEG system) and the cathode over the lateral right frontal area at F8. Pre-treatment clinical and neurocognitive variables were examined as predictors of efficacy.

Results: Concurrent antidepressant medication use [F(60) = 7.82, p = <.01] predicted antidepressant response to active tDCS treatment. In a multivariate model, Total Speed from the Ruff 2 & 7 Selective Attention Test also predicted response [β = .25, p < .05]. Secondary repeated measures analyses investigating Total Speed Group (tertiles: between subject factor), condition (active and sham) and Time (pre-treatment, post 10, post 20 tDCS) revealed a statistically significant Time by Total Speed Group interaction [F(200) = 6.08, p = <.001]. Post hoc tests found that participants in the fastest Total Speed Group showed greater efficacy in both tDCS conditions (p < .05).

Conclusions: Better processing speed/concentration was associated with enhanced antidepressant efficacy to tDCS. Further investigation is warranted to determine the underlying mechanisms of pre-treatment neurocognitive functioning and tDCS related antidepressant effects

Supported By: Stanley Medical Research Foundation

Keywords: transcranial direct current stimulation, cognition, mood, depression

642. Cortical Evoked Response as Objective Measure of Target Engagement in Subcallosal Cingulate Deep Brain Stimulation for Treatment Resistant Depression

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Background: A challenge to effective dissemination of SCC-DBS for treatment resistant depression is the absence of objective biomarkers to guide the selection of stimulation parameters, such as the active contact location and stimulation magnitude. We previously assessed the viability of an event-related potential (ERP) approach to characterize the distributed cortical response to SCC-DBS parameters. The current research uses quantitative methods to identify variance in the DBS ERP that can be attributed to individual differences in structural connectivity and modeled neural elements within the activated tissue.

Methods: Four patients underwent simultaneous dense array electroencephalography (256-channels) and low frequency (2Hz) SCC-DBS at four time points. We investigated ERP indices on the scalp surface and in source models with three experimental contrasts: 1) optimal versus non-optimal contact locations, 2) increasing levels of voltage, and 3) over time in treatment. White matter architecture was modeled in individuals using probabilistic tractography and restricted computational activation modeling.

Results: Variance in the scalp recorded ERP reflected individual differences in structural connectivity and optimal contact placement at the convergence point of four white matter fiber tracts. A non-linear relationship of ERP and source magnitude with increased voltage reflected differential activation of white matter fiber tracts. The latency and magnitude of a posterior feature changed over time in treatment, suggestive of neural remodeling.

Conclusions: Our results demonstrate a stimulation-locked, cortical evoked potential following SCC-DBS that may serve as an objective method for reliable device configuration and treatment optimization with respect to individual differences in structural and functional anatomy.

Keywords: Treatment Resistant Depression, Deep Brain Stimulation, Biomarkers, Electroencephalography, treatment algorithm

643. Sustained Improvement in Mood after 3 Days of Low Field Magnetic Stimulation in Subjects with Bipolar Depression

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McLean Hosital
Background: LFMS is a treatment for depression that uses a low field, high frequency stimulation. Immediate improvement in mood has been observed in subjects with bipolar and major depression, often occurring within minutes. No reports have yet been made of the duration of these effects on mood or on the effects of multiple treatments.

Methods: 50 subjects suffering from depression and diagnosed with Bipolar Disorder (ages 21-60, 10F/14M sham, 12F/14M active) were treated with active or sham LFMS for 3 consecutive days in a parallel, randomized, double-blinded study, with a follow-up visit at 1 week and phone calls at 2 and 3 weeks. The Montgomery-Asterg Depression Rating Scale was assessed at each contact along with other exploratory measures. The primary measure was change in MADRS from the pre-treatment screening visit to the one week follow-up visit. Data were analyzed using a one-sided regression test using Stata, covaried with the pre-treatment MADRS value.

Results: Improvement in mood ($t=-1.68, p<0.05$) was observed in this population. A mean change in MADRS score of $-9.75$ was observed for sham, and a change of $-14.0$ points was observed for active LFMS. A strong placebo effect was observed during the treatment period, and separation between the treatment groups is evident only after treatment has ceased.

Conclusions: These results suggest that the mood improving effects of LFMS may last up to a week in responding subjects. This study was limited to subjects with bipolar disorder. The strong placebo effect demonstrates the particular challenge when studying fast acting antidepressants.

Supported By: Depressive and Bipolar Disorders Alternative Treatment Foundation, McLean Hospital, Tal Medical.

Keywords: Bipolar, Depression, LFMS, Stimulation

644. Neurocognitive Effects of Transcranial Direct Current Stimulation (tDCS) in Unipolar and Bipolar Depression: Results from an International Randomized Controlled Trial

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Background: Transcranial direct current stimulation (tDCS) has been found to have antidepressant effects, and may have beneficial neurocognitive effects. However, prior research discrepancies produce uncertainty regarding the neurocognitive effects of tDCS. The purpose of this study was to determine the neurocognitive effects of tDCS.

Methods: The study was a triple-masked, randomized, controlled design across six international academic medical centers. Participants were randomized to active (2.5milliamperes for 30 minutes) or sham (3microamperes, and two 60-second current ramp-ups of 1 and 0.5milliamperes) tDCS for 20 sessions. The anode was centered over the left DLPFC at F3 (10/20 EEG system) and the cathode over the lateral right frontal area at F8. Participants completed clinical and neurocognitive assessments before and after the tDCS course. Mixed effects repeated measures analyses were conducted with factors Time and Condition, including mood ratings as a covariate.

Results: The study randomized 130 participants. Across the sample, there was a significant interaction trend for cognitive flexibility ($p<0.06$) and visual attention ($p<0.06$). Post hoc tests revealed significantly improved cognitive flexibility ($p<0.05$) and visual attention ($p<0.05$) with active and sham TDCS, respectively. For patients with bipolar depression, there was a significant interaction trend for auditory attention and working memory ($p=0.08$). Post hoc tests showed significant improvement only with sham tDCS ($p<0.05$).

Conclusions: These findings suggest that tDCS has positive neurocognitive effects in unipolar and bipolar depression, after accounting for mood effects. Moreover, unique tDCS stimulation paradigms may have differential neurocognitive effects. Future research is warranted to determine optimal stimulation paradigms to enhance neurocognitive function.

Supported By: Stanley Medical Research Institute

Keywords: transcranial Direct Current Stimulation, neurocognitive outcome, Depression, Bipolar Disorder

645. Neural, Cognitive, and Clinical Effects of Prefrontal Cortex Stimulation in Depression Combined with Psychological Therapy: A Double-Blind Randomized Controlled Trial

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Background: Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) has recently shown efficacy as a treatment for depression. We combined tDCS with psychological therapy to determine whether tDCS of the DLPFC could enhance therapeutic outcome in depression.

Methods: We conducted a double-blind, randomized controlled trial of tDCS in patients with depression receiving a course of CBT (N=35). Patients received eight 20-minute sessions of tDCS directly preceding CBT for 8 weeks. The primary outcome was interviewer-rated depression scores. Secondary outcome measures included functional magnetic resonance imaging (fMRI) scans prior to and following treatment to measure DLPFC activation during working memory. We compared fMRI results with matched healthy controls (N=30).

Results: The intervention was relatively well tolerated, with 17% attrition. Using an intent-to-treat analysis, 20% more
patients responded to CBT with tDCS (9/18) than CBT with sham stimulation (5/17; OR = 2.4), though this difference did not achieve statistical significance ($X^2 = 0.214, p = 0.605$). Depressed patients initially showed blunted activation in the DLPFC compared to healthy controls ($p < 0.05$). Following the trial, DLPFC activity increased substantially in the depressed group ($p < 0.001$). However, there was no effect of tDCS on activation ($p > 0.2$). Irrespective of stimulation condition, initial DLPFC activity was positively associated with a future reduction in depression symptoms ($p < 0.05$).

**Conclusions:** The current findings provide support for the safety and tolerability of tDCS to augment psychological interventions. They do not provide strong support for clinical efficacy of the augmentative intervention, but they suggest that the DLPFC may be involved in the beneficial effects of CBT.

**Supported By:** NARSAD; Wellcome Trust; Brain Research Trust

**Keywords:** tDCS, Depression, fMRI, CBT, Prefrontal Cortex

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**646. The Effect of rTMS on Cerebral Blood Flow in Treatment Resistant Depression in Youth**

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University of Calgary

**Background:** Current treatment options for major depressive disorder (MDD) in youth are limited both in response and durability. Repetitive transcranial magnetic stimulation (rTMS) is an emerging as a novel intervention for treatment-resistant major depressive disorder (TRD) in youth. We hypothesize that the target site for rTMS, left middle frontal gyrus, will differ in cerebral blood flow (CBF) between responders and non-responders to treatment.

**Methods:** Twenty-four patients with TRD were treated with rTMS over a period of three weeks: 15 sessions, high-frequency rTMS (120% RMT, 3000 pulses per session). Resting state CBF was acquired using arterial spin labeling MRI prior to and after treatment and for ten healthy controls. Response to treatment was defined as a 50% decrease in Hamilton Depression Rating Scale (Ham-D) scores. Statistical Parametric Mapping (SPM) software was used to pre-process data and perform statistical analysis. A small volume correction was applied to the region of interest.

**Results:** At baseline, non-responders had greater CBF compared to responders in the left middle frontal gyrus ($p = 0.002$). Non-responders also had greater CBF than controls at baseline, in the left middle frontal gyrus ($p = 0.004$). There were no differences between responders and controls at baseline.

**Conclusions:** This is the first study to examine the effect of rTMS treatment on cerebral blood flow in adolescents. Our preliminary analyses suggest greater CBF in the left middle frontal gyrus may be a biomarker indicative of a lack of response to rTMS treatment in adolescents with TRD.

**Supported By:** Children’s Hospital Aid Society

**Keywords:** rTMS, Adolescent Depression, Cerebral blood flow, DLPFC, Biomarkers

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**647. Glutamate and Response to Repetitive Transcranial Magnetic Stimulation in Youth with Treatment Resistant Depression**

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University of Calgary

**Background:** Glutamate plays a central role in the pathophysiology of depression and is a target for modulation by repetitive transcranial magnetic stimulation (rTMS). We evaluated the effect of high-frequency (10Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC) in adolescents and young adults with treatment-resistant major depressive disorder (TRD) on the concentration of DLPFC glutamate as assessed with short echo proton magnetic resonance spectroscopy (1H MRS).

**Methods:** TRD youth between the ages of 12 and 21 years participated in a 3-week open-label treatment study of rTMS, with 1H MRS measurements of DLPFC glutamate levels at baseline and following 3 weeks of the rTMS intervention. We applied rTMS for 15 consecutive weekdays (120% resting motor threshold; 40 pulses over 4 seconds [10 Hz]; inter-train interval, 26 seconds; 75 trains; 3000 pulses). Treatment response was defined as a 50% or greater reduction in Hamilton Depression Rating Scale (Ham-D) scores.

**Results:** Twenty-three youth with TRD (13 males) completed the rTMS intervention. At baseline, responders had 19.27% ($p = 0.02$) lower DLPFC glutamate concentrations than non-responders. DLPFC glutamate increased by 10.35% ($p = 0.01$) in responders and decreased by 7.39% ($p = 0.004$) in non-responders. Ham-D Change in depression severity (Ham-D) was significantly predicted by the change in glutamate concentrations ($\beta = -13.05, p = .004$).

**Conclusions:** These results implicate glutamate in the mechanism of action of rTMS for TRD in youth and as a potential predictive biomarker. This warrants further investigation in larger samples in biomarker enriched trial designs.

**Supported By:** Children’s Hospital Aid Society

**Keywords:** Glutamate, rTMS, Adolescent Depression, DLPFC, Biomarkers

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**648. Can Transcranial Direct Current Stimulation (tDCS) Modulate the Affective Component of Chronic Low Back Pain (CLBP)?**

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**Background:** Pain has both nociceptive (sensory) and emotional (affective) components (IASP 2016). CLBP remains a significant medical burden; annual prevalence is 15%-45%
Methods: We performed a multi-site, double-blinded, randomized placebo-controlled trial of tDCS targeting left dorsal anterior cingulate cortex (dACC)—a node in the pain network—in 21 CLBP participants. Each participant received 10 daily sessions of sham or cathodal tDCS (thought to reduce cortical excitability) at 2 mA for 20 minutes. Saline-soaked sponge electrodes (5x7 cm) were placed at FC1 (per the 10-20 EEG system) and the contralateral mastoid process (return electrode). Participants rated pain intensity, disability, and acceptance during and after treatment.

Results: Interim analysis failed to demonstrate separation between sham and active tDCS for any outcome measure (all marginal effect size: t<1.7, p>0.1). Futility analysis suggests at least 46 additional participants are needed to detect a statistically-significant stimulation-related effect.

Conclusions: These preliminary results do not suggest that 10 daily sessions of cathodal tDCS targeting left dACC significantly improve the affective symptoms of CLBP. Future better-powered studies should consider other cortical targets, different stimulation parameters, high-density electrode arrays, and combining tDCS with psychotherapy such as CBT.

Supported By: NARSAD (PI: Mariano)

Keywords: tDCS, chronic pain, chronic low back pain, Neuromodulation, transcranial Direct Current Stimulation

649. Trajectories and Changes in Individual Items of Positive and Negative Syndrome Scale among Schizophrenia Patients Prior to Impending Relapse

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Background: Schizophrenia is a devastating illness characterized by frequent relapse of acute psychotic symptoms. Effective early detection of relapse symptoms may offer early interventions to prevent impending relapse. To provide a basis for developing technology-enabled remote assessment solutions for monitoring and predicting relapse, we analyzed data from 3 internal Janssen studies to identify individual items of Positive and Negative Syndrome Scale (PANSS) that changed the most prior to relapse and to understand exactly when these symptoms manifested.

Methods: Relapse was defined as having either a psychiatric event (hospitalization, suicidal or homicidal ideation, or violent behavior) or a significant increase in the PANSS total score or several pre-specified individual PANSS item scores. Linear and non-linear mixed effect models were applied to model the trajectories of individual PANSS items from a stable state to the time of relapse.

Results: Among the 267 relapsed patients, a subset of 7 PANSS items had an average more than 1-point of increase at relapse from randomization. These 7 PANSS items included P1 [delusions] (mean change (standard error): 1.53(0.08)), P6 [suspiciousness] (1.49(0.08)), P3 [hallucinations] (1.44(0.09)), G2 [anxiety] (1.32(0.07)), P4 [excitement] (1.29(0.07)), G4 [tension] (1.24(0.07)), and P2 [conceptual disorganization] (1.12 (0.07)). The trajectories of these items suggested that these items started to increase 7-10 days before relapse and reached on average 1-point of increase 0.3~1.2 days before relapse.

Conclusions: Our results indicated that a subset of PANSS items (P1, P2, P3, P4, P6, G2, and G4) could be used to develop remote assessment solutions for monitoring and predicting relapse in schizophrenia patients.

Keywords: Schizophrenia, Relapse Prevention, Positive and Negative Syndrome Scale, Individual Items, Remote Assessment Solution

650. Effects of Transcranial Direct Current Stimulation (tDCS) on Cognitive Function in Schizophrenic: Different Neural Activation under Different Task Demands

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Background: Schizophrenia is characterized by persistent cognitive deficits. Transcranial direct current stimulation (tDCS) is a safe and noninvasive brain stimulation method, and several studies showed that it can improve cognitive function in schizophrenia. The current study was a double-blind sham-controlled study to investigate neural alternations before and after tDCS under different task demands.

Methods: 26 schizophrenic inpatients, participated in double-blind study of 10 sessions of active or sham tDCS (active tDCS for 20 min, 2 mA), with anode placed over the left DLPFC and the cathode over contralateral supraorbital ridge. Before and after 10 sessions of tDCS, fMRI were scanned under 0-back and 2-back working memory tasks was analyzed to check the difference between low and high level tasks, and RS connectivity will be analyzed.

Results: Task activation increased in right middle frontal gyrus (BA 45, 10) after 10 tDCS sessions for the 0 back condition. No changes were found under the 2 back condition. We are currently analyzing RS connectivity changes, and these results will also be presented.

Conclusions: In this sample, the positive finding under 0 back task suggest that 10 sessions of tDCS elicits changes in frontal lobe cortical recruitment during the lower-demand cognitive task, but not a higher demand task. This intriguing pattern of findings will be discussed in terms of models of cognitive deficit.
651. Effect of Bright Light Therapy on White Matter Abnormalities following a Mild Traumatic Brain Injury

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**Background:** White matter (WM) integrity still needs to be explored to determine the structural and cognitive impairment following an mTBI. We aim to explore such WM abnormalities and analyze the impact of morning bright (amber/blue) light therapy (ALT/BLT) on WM integrity.

**Methods:** 39 healthy-controls (HCs) and 28 mTBI survivors (before and after six weeks of either ALT or BLT) underwent diffusion tensor imaging. Raw quantitative anisotropy (QA), normalized QA (NQA) and isotropic (ISO) diffusion were estimated for 11 regions of interest (ROIs): the dorsal-lateral prefrontal cortex (DLPFC), genu, splenium and body of the corpus callosum (CC), the left/right uncinate fasciculus (L/R UF) and the thalamus.

**Results:** Using two-sample t-tests (p < 0.05), we found that all ROIs (a) had significantly higher QA and (b) except the splenium, the LSLF and the thalamus, had significantly higher ISO for mTBI than HCs. There was no significant improvement in NQA for any ROI following ALT. Following BLT, four ROIs (the body of CC, the L/R UF and the LACR) showed significant decrease in NQA (paired t-test, p < 0.05) and three ROIs (the body of CC and the L/R UF) showed significant decrease in QA (paired t-test, p < 0.05), we found that (c) except the body of CC and the L/R UF, there was no significant change in week 1, week 2 and week 3 readings.

**Conclusions:** BLT helped to improve WM integrity and behavior of mTBI survivors, indicating that BLT can be an effective treatment for mTBI survivors.

**Supported By:** DOD W81XWH-11-1-0056

**Keywords:** Sleep Disorders, Diffusion Tensor Imaging (DTI), Mild Traumatic Brain Injury, Light Therapy, Anisotropic-Diffusion

652. Novel Complementary and Alternative Mindfulness Based Intervention: Therapeutic Approach to Manage Substance Use Disorders and Posttraumatic Stress Disorder

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**Background:** Relapse is a core feature of substance use disorders (SUD). Intentional slower breathing or "intentional respiratory rate variability" (IRRV) by the aid of Rhemercise (a new exercise manual) may be an effective therapeutic approach for well-being. IRRV can increase Heart Rate Variability (HRV) and that HRV is the biomarker of overall well-being. We hypothesize that increased HRV could decrease craving creating relapse prevention strategy. We hypothesize that IRRV increases HRV.

**Methods:** Fitness Assessment Chair Test (FACT) performed at the College of Physiotherapy, Christian Medical College, Ludhiana, Punjab, India. The research involved 15 physiotherapy students and interns 19-25. The progression of fitness was assessed using the FACT, over 3 weeks. The statistical F test, ANOVA, was used to compare the data and post hoc test, Tukey's test, to compare the pairwise count. This small sample study showed significant changes in week 1, week 2, and week 3 readings.

**Results:** F test (ANOVA) is used to compare the counts. Calculated Test statistics (F test) value 20.447 is more than the table value 3.220. So the difference is significant. Null Hypothesis is rejected there is significant change in week 1, week 2 and week 3 readings with respect to 10 seconds readings.

**Conclusions:** FACT is a form of Rhemercise that could increase physical well-being. We hypothesize that IRRV by YR can increase HRV and subsequently decrease craving for illicit drugs. IRRV could be a therapeutic approach to prevent relapses in people with SUD and PTSD.

**Keywords:** YoHA Rhemercise, Substance Use Disorder, Posttraumatic Stress Disorder, IntentionalRespiratory Rate Variability, Heart Rate Variability

653. Can What Goes up Come Back Down? The Effects of DCS on Individual Differences in Relapse of Fear

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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; animals with a slow rate of extinction are more vulnerable to relapse than animals with a fast rate of extinction. Here we examined individual differences in the efficacy of D-Cycloserine (DCS) in reducing relapse in a setting where both groups show marked relapse.

**Methods:** Experimentally-naïve adult male rats received pairings of a white noise CS with a shock US, extinction to a criterion followed by an injection of DCS or Saline, and then tested for renewal of fear. The number of blocks to reach criteria in extinction was used to classify animals as “fast” or “slow” extinguishers. CS-elicited freezing was taken as the measure of fear, and the results below are in terms of percentage of time spent freezing.

**Supported By:** Shanghai Mental health institute, internal funds; CSC.

**Keywords:** tDCS, Working memory, Neuroimaging, Randomized controlled trial, Schizophrenia
654. Investigation of Modulation of mGluR4 as a Novel Pharmacological Approach to the Treatment of Maladaptive Impulsivity

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Background: Maladaptive impulsivity is a core and trans-diagnostic symptom spanning several neuropsychiatric disorders. While some treatment options are currently available there remains a high unmet medical need; this, in combination with well-established and closely aligned clinical and pre-clinical tests for the measurement of impulsivity, makes the identification of novel therapeutic concepts for its treatment an important as well as feasible endeavor. These findings show that while both “fast” and “slow” extinguishers exhibit relapse of fear under some conditions (i.e., ABA), “fast” extinguishers are more responsive to the relapse-attenuating effects of DCS. Our findings have implications for identifying those most at risk for relapse following treatment and provide insight into sub-populations for whom pharmacological adjuncts to therapy might be more/less effective.

Keywords: D-Cycloserine, Fear Extinction, Individual differences, Renewal, Relapse

Results: Both “fast” and “slow” extinguishers show ABA renewal, with no significant differences between groups that were injected with Saline (M=83.6% vs 94.7%, t14=−1.7, p=.11). However, when injected with DCS after extinction, “fast” extinguishers showed significantly less ABA renewal than “slow” extinguishers (M=58.8% vs 96.4%, t14=−3.9, p<.01).

Conclusions: Both Rats were trained in the 5-CSRTT to investigate the effect of the positive allosteric mGluR4 modulator, 4-((E)-styril)-pyrimidin-2-ylamine (Cpd11), either alone or in combination with the D2 receptor antagonist eticlopride, on motor impulsivity. Cpd 11 and eticlopride were administered systemically at doses of 40-80mg/kg and 0.005-0.02mg/kg respectively.

Results: Administration of Cpd11 dose-dependently augmented impulsivity in the 5-CSRTT, as measured by an increase in premature responses. Pre-treatment with eticlopride selectively attenuated Cpd11 effects, at doses that had no effect on behavioral performance when administered alone.

Conclusions: These findings demonstrate that positive modulation of the activity of mGluR4 exerts a significant effect on motor impulsivity. Moreover the results suggest that, via modulation of the indirect striato-pallidal-sub-thalamic pathway, negative modulation of mGluR4 could be a novel approach to ameliorate impulsive behavior in neuropsychiatric disorders in which maladaptive impulsivity plays a role.

Supported By: CNS Diseases Research, Boehringer Ingelheim Pharma, Germany

Keywords: Impulsivity, mGluR4, novel drug targets, Translational research

655. Assessment of Efficacy and Psychotomimetic Effects of Ketamine in the Mouse

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Background: Psychotomimetic effects of ketamine were described at therapeutically active doses in patients suffering from treatment resistant depression. In this study we investigated in C57 mice the effects of ketamine on an efficacy associated read-out, and various behaviors reflecting psychotomimetic effects.

Methods: The antidepressant-like effect was evaluated using the forced swim test (FST). To assess “dissociative” effects, we developed a test battery which allows the observation of various behaviors in the mice which could be linked with human psychotomimetic effects. In detail, we assessed ataxia, tremor, hyperactivity, Straub tail and stereotypy.

Results: Ketamine was inducing “psychotomimetic” effects in a dose dependent manner. First effects were detectable at 20 mg/kg. Surprisingly, efficacy of ketamine in the FST was observed at 3 mg/kg separating efficacy versus psychotomimetic effects by a factor of >6. Ketamine was also increasing locomotion already at 10 mg/kg demonstrating that the induction of hyperlocomotion in mice is the first signal towards tolerability side effects.

Conclusions: The detailed characterization of ketamine in the psychotomimetic battery allowed the identification of behaviours which could contribute to the dissociative effects as observed in human. However, while in the mouse efficacy and tolerability separated by a factor of 3 based on the hyperlocomotion assay and a factor of 6 based on the induction of psychotomimetic effects in human psychotomimetic effects are observed at the efficacious dose. These data may challenge the relevance of the mouse to predict efficacy/tolerability for NMDA-R antagonists.

Keywords: Ketamine, psychotomimetics, NMDA antagonists, NR2B, Antidepressant

656. Different Effects of NR2B Antagonists on Behavior Paradigms in Mice

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Boehringer-Ingelheim

Background: NR2B subunit-specific negative allosteric modulators (NAM) have raised interest for their potential to
treat patients suffering from depression with efficacy similar to the unselective NMDA-R antagonist ketamine but with improved tolerability. Two different NR2B NAMs were explored in clinic: traxoprodil and Cerc-301. In this study we investigated both compounds for efficacy and tolerability in rodents.

**Methods:** All animal studies were run in male C57 mice. The antidepressant-like effect was evaluated using the mouse forced swim test (FST). To assess dissociative effects, we characterized these compounds in a test battery assessing psychotomimetic behavior. In detail, we assessed ataxia, tremor, hyperactivity, Straub tail, jumping and stereotypy.

**Results:** Cerc-301 (2 mg/kg) and traxoprodil (6 mg/kg) were found active in the FST. Interestingly, traxoprodil showed effects only on stereotypies at 20 mg/kg thereby separating from efficacy by a factor of >3. In contrast, the second NR2B NAM Cerc-301 dose dependently induced hyperactivity and stereotypy in our test system already at 2 mg/kg with increasing magnitude up to the highest dose tested (18 mg/kg).

**Conclusions:** The detailed characterization of two different NR2B NAMs on an efficacy readout (FST) and psychotomimetic test battery demonstrate that the qualitative effects of NR2B NAM are similar across molecules. In contrast, the quantitative efficacy versus tolerability window differs across molecules and additional parameter on top of the potency of a NR2B NAM may contribute to this difference.

**Keywords:** NR2B, FST, depression, psychotomimetic, traxoprodil

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657. Effects of Imipramine, Scopolamine, Ketamine, NR2B and P2X7 Antagonists in a Chronic Model of Stress (CMS)-Induced Anhedonia

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**Background:** It is well accepted that it is difficult to model affective disorders. Since anhedonia is a major clinical feature of depression, the CMS model of anhedonia appears to be a relevant test system. The CMS-induced anhedonia can be reversed following a chronic application of established antidepressants but not by drugs devoid of clinical activity in depressed patients.

**Methods:** Rats were exposed to the CMS procedure for 7 weeks. During this time their consumption of 1% sucrose solution was measured at weekly intervals. After initial 2 weeks of stress the animals showed a stable decrease of their intakes and were administered with reference antidepressant, imipramine (10 mg/kg; i.p.) or test compounds across different target classes. All compounds were also dosed to the non-stressed rats and body weights were measured during the entire experiment.

**Results:** Treatment with imipramine reversed sucrose consumption deficit after 4-5 weeks of drug treatment. Scopolamine (1.5 mg/kg; i.p.) exhibited a rapid onset of action with complete reversal of the deficit after 1 week of dosing. Ketamine’s (10 mg/kg; i.p.) onset of effect was more gradual. In addition, CP-101,606 (NR2B antagonist) also produced rapid (within 1 week) onset of action and full reversal of anhedonia. In addition to these mechanisms, we tested a P2X7 (neuropathic) antagonist at 1 mg/kg (p.o.) that was also effective, albeit with a slower onset of action than CP-101,606 or scopolamine.

**Conclusions:** The chronic model of stress-induced deficits in sucrose intake can be reversed by a wide variety of mechanisms, albeit with different degrees of onset of action.

**Keywords:** Chronic Stress, scopolamine, Ketamine, P2X7R, NMDA antagonists

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658. Metformin Enhances Antidepressant Response Rate to Ketamine in a Rodent Model of Antidepressant Treatment Resistance

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**Background:** The neuroendocrine link between stress, depression, and metabolic dysfunction may play an important role in antidepressant non-response. Chronic stress and allostatic overload impair insulin sensitivity, glucose homeostasis, mitochondrial function, and an individual’s capacity to respond to cellular challenges. We have previously shown that insulin signaling pathway activation directly correlates with antidepressant response to ketamine in antidepressant-resistant rats. This project aimed to determine the synergistic therapeutic effect of metformin on ketamine’s antidepressant response in these animals.

**Methods:** Rats were administered adrenocorticotropic hormone (ACTH) (100ug/day, 14 days) to establish a tricyclic antidepressant-resistant phenotype. Rats were administered control vehicle saline or ketamine (10mg/kg) and/or metformin (200mg/kg). Rats then underwent the open field and forced swim test. Before and after behavioral testing, blood was collected for measurement of insulin and glucose levels.

**Results:** Results demonstrate that metformin+ketamine significantly reduced immobility during the forced swim test in ACTH-pretreated rats (p<0.001), matching the antidepressant effect of ketamine-resistant animals pretreated with ACTH (~50%). Notably, the response rate for metformin+ketamine was significantly higher than for ketamine alone (p<0.05). Immediately following forced swim, these animals also had significantly higher glucose levels relative to ketamine responders (p<0.01), ACTH controls (p<0.05), and naive controls (p<0.001). Regressional analyses revealed a significant negative relationship
between glucose and insulin following metformin and ketamine administration (p<0.01).

Conclusions: These results suggest an important relationship between stress, insulin, and glucose homeostasis, which may be a critical mediator of ketamine’s antidepressant action. This presents the possibility that metformin may be a useful co-treatment to improve response rates to ketamine.

Supported By: State of Minnesota

Keywords: Ketamine, Metformin, Insulin, Antidepressant, Treatment Resistant Depression

659. Metabolomics Analysis of Tricyclic Antidepressant Treatment Resistance in a Rodent Model: Disrupted Energy Metabolism Mitigated by Lithium Augmentation

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Background: Major depressive disorder and bipolar disorder, are often comorbid with significant metabolic disturbances. We aimed to identify key brain- and blood-based metabolic markers associated with development of tricyclic antidepressant treatment resistance in a rodent model. Additionally, we explored the metabolomic profile associated with antidepressant response to lithium augmentation in these animals.

Methods: Tissue from the infralimbic and prelimbic cortices, as well as serum samples, from tricyclic antidepressant-resistant rats pretreated with adrenocorticotropic hormone (ACTH; 100ug/1mL/day; 14 days) and saline treated control animals (0.9% saline/1mL/day; 14 days). Animals received imipramine (10mg/kg), saline (0.9%) or imipramine (10mg/kg) + lithium (100mg/kg) (ACTH-treated animals only) antidepressant treatments prior to open field and forced swim tests. Tissues were collected postmortem, 30 minutes after forced swim, and examined via non-targeted mass spectrometry–based comprehensive metabolic profiling. Metabolicomic differences were examined for the following groups: (1) saline-pretreated v’s ACTH-pretreated; (2) Saline-imipramine v’s ACTH-imipramine; ACTH-imipramine v’s ACTH-imipramine-lithium. Gender effects were also explored.

Results: ACTH treatment blocked imipramine-induced immobility in the FST. In contrast, lithium+ imipramine were effective in reducing immobility behavior in these animals. Key metabolite differences observed consistently across brain and blood samples were identified in pathways related to DNA breakdown, oxidative stress and neurotransmitter metabolism. The addition of lithium to imipramine treatment altered levels of metabolites involved in fatty acid metabolism, catabolic processes, and purigenic signaling.

Conclusions: The current study documented a synergy between aripiprazole and escitalopram in increasing the hippocampal tonic activation of 5-HT1A receptors after 14 days of administration. These results showed an enhanced 5-HT1A neurotransmission in the hippocampus which occurred in the presence of normal firing activity of 5-HT neurons. Neither of the medications increased noradrenergic neurotransmission.

Supported By: Ontario Brain Institute

Keywords: aripiprazole, Major Depressive Disorder (MDD), SSRI, Treatment Resistant Depression, Monoamines

660. Effect of Combining Aripiprazole with Escitalopram on Serotonergic and Noradrenergic Neurotransmission in the Rat Hippocampus

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Background: Aripiprazole is an atypical antipsychotic approved as an adjunct for inadequate response to antidepressants in the treatment of major depressive disorder. Addition of aripiprazole to escitalopram reverses the inhibitory actions of escitalopram on firing activity of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) neurons. This study investigated the postsynaptic neurotransmission of the previously studied monoamines systems.

Methods: Electrophysiological recordings of hippocampus CA3 pyramidal neurons were conducted in anaesthetized Sprague-Dawley rats after 2 and 14 days of treatment. Aripiprazole and escitalopram (2 and 5 mg/kg/day; subcutaneous injection and implanted osmotic minipumps, respectively) were delivered alone or in combination. Serotonergic and noradrenergic neurotransmission were assessed by measuring the tonic activation of 5-HT1A and α1- and α2-adrenergic receptors.

Results: Fourteen-day escitalopram and combined escitalopram-aripiprazole administration significantly inhibited the 5-HT transporter activity. While neither 2- and 14-day administration of escitalopram nor aripiprazole significantly altered tonic activation of 5-HT1A receptors, combination of aripiprazole with escitalopram for 14 days significantly increased tonic activation of 5-HT1A receptors of the pyramidal neurons compared to the control group. Fourteen days of the same drug regimens neither changed the activity of the NE transporter nor the tonic activation of α1- and α2-adrenergic receptors.

Conclusions: The current study documented a synergy between aripiprazole and escitalopram in increasing the hippocampal tonic activation of 5-HT1A receptors after 14 days of administration. These results showed an enhanced 5-HT1A neurotransmission in the hippocampus which occurred in the presence of normal firing activity of 5-HT neurons. Neither of the medications increased noradrenergic neurotransmission.

Supported By: University of Ottawa Institute of Mental Health Research

Keywords: aripiprazole, Major Depressive Disorder (MDD), SSRI, Treatment Resistant Depression, Monoamines

661. Divergent Effects of Acute and Repeated Quetiapine Treatment on Dopamine System in Normal and Chronic Mild Stress Induced Hypodopaminergic States

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Background: The dopamine D2 receptor antagonists (D2RAs) quetiapine and lurasidone are effective antidepressant agents. However, an antidepressant effect of a dopamine antagonist seems paradoxical given the decreased dopamine system function in depression. Here we examined the electro-physiological impact on ventral tegmental area (VTA) dopamine neurons of acute and repeated administration of quetiapine at antidepressant doses in normal rats and those exposed to the chronic mild stress (CMS) rodent depression model, the latter representing the hypodopaminergic state observed in patients with depression.

Methods: Rats (N=74) exposed to 5-8 weeks of normal or CMS conditions received quetiapine 10 mg/kg i.p. acutely or repeated for 21 days. Single unit extracellular recording of identified VTA dopamine neurons was performed to assess firing properties including the number spontaneously active (population activity), average firing rate, and amount of burst firing.

Results: Acute quetiapine increased dopamine neuron population activity in normal but not in CMS-exposed rats (2-way ANOVA p<0.05). Conversely, repeated quetiapine increased VTA dopamine neuron population activity to normal levels in CMS-exposed rats, but had no persisting effects in normal rats (2-way ANOVA p<0.05). Average firing rate and amount of bursting were not significantly altered in any group.

Conclusions: These data suggest that D2RAs such as quetiapine may exert their antidepressant actions via differential effects on the dopamine system in a normal vs. hypoactive state. Restoration of dopamine neuron responsivity by normalizing stress-induced decreased population activity therefore could be a primary therapeutic action of D2RAs. These results highlight the importance of evaluating medications in both normal animals and disease models.

Supported By: F30 MH105199, R01 MH101180
Keywords: Dopamine, Atypical Antipsychotics, Animal Models, Electrophysiological Single Unit Recordings

662. Ketamine and Rapastinel Effects on Glutamate Cycling
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Background: Increases in glutamate neurotransmission are believed to underlie many of the effects of NMDA receptor targeting drugs. Ex vivo 1H-[13C]-NMR studies can be employed to examine pharmacological effects on glutamate metabolism and cycling. The objective of this study was to examine the short term effects of rapastinel (GLYX-13) in comparison to ketamine in a rodent model.

Methods: Five groups [Vehicle (saline), GLYX-13 (3,10, and 30 mg/kg) and ketamine (10mg/kg), (n=16/control group and n=8/treatment groups)] of rats were administered studies drugs IV via tail vein T-10mins prior to [1,6-13C2]glucose that was also infused via tail vein at T=0. Animals were euthanized after an 8-minute glucose infusion. Processing and isotopic measures of hippocampal and mPFC tissue, and blood samples were made as described in (Chowdhury et al, 2016).

Results: Consistent with previous reports (Chowdhury 2012 and 2016) sub-anesthetic ketamine treatment produced statistically significant, large to very large effect increases on the labeling of all 3 metabolites in the mPFC (Glu d1= 1.2; GABA d1=1.0; and Gln d=1.9) and in the hippocampus (Glu d= 1.1; GABA d1=1.3; and Gln d=1.3). Rapastinel treatment did not have a statistically significant effect over the saline control treatment on any of the metabolites in either brain region.

Conclusions: Consistent with previous reports, Ketamine increased 13C enrichment of GABA, glutamine and glutamate, suggesting stimulation of rapid increases in amino acid neurotransmitter cycling. In contrast, rapastinel did not produce these effects, suggesting the two drugs have differential effects on NMDA receptor modulation of glutamate neurotransmission.

Supported By: Naurex (which was acquired by Allergan in August 2015)
Keywords: glutamate or GABA, MRS, Magnetic Resonance Spectroscopy, Ketamine, Rapastinel

663. An Examination of the Mechanism of Action of Fenfluramine in Dravet Syndrome: A Look beyond Serotonin
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Background: Fenfluramine (FFA) provides unique antiepileptic activity in Dravet syndrome (DS) with a high degree of seizure freedom and prolonged duration of effect. The antiepileptic activity of FFA is believed to be mediated through serotonin release and serotonin receptor agonist activity. Although limited data in the literature suggest that other serotonergic drugs (SSRIs) have some antiepileptic activity, they lack a similar clinical effect to FFA. Therefore, we examined other potential receptor mechanisms that might contribute to FFA’s effectiveness in DS.

Methods: Forty-seven receptors were identified in the literature as being associated with seizures. These were screened in in vitro receptor binding assays with racemic FFA, the metabolite norfenfluramine (nFFA), or their enantiomers. Receptors to which binding occurred were further tested in functional assays using isolated CHO, HEK-293 cells, or guinea pig vas deferens tissue.

Results: Binding of FFA or nFFA and their enantiomers occurred at the µ2-adrenergic, muscarinic M1, and Sigma 1 and 2 receptors with Ki values ranging from 0.277 µM to 14 µM. Both (+) and (-) enantiomers of FFA and nFFA demonstrated antagonist activity at the µ2-adrenergic and muscarinic M1 receptors at concentrations of 49 – 95 µM. Racemic fenfluramine and its enantiomers appeared to act as positive allosteric modulators of Sigma at concentrations of 5.0 – 5.6 µM, while norfenfluramine and its enantiomers appeared to act as inverse agonists of Sigma starting at concentrations of 5 µM.

Conclusions: Fenfluramine’s antiepileptic mechanism of action may be mediated not only by serotonin but also by adrenergic, muscarinic, or sigma receptors.
Keywords: serotonin, Dravet Syndrome, epilepsy, fenfluramine, mechanism of action
664. Selectivity of Valbenazine (NBI-98854) and Its Major Metabolites on Presynaptic Monoamine Transport
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Background: Vesicular monoamine transporters (VMATs) are intracellular proteins that regulate the packaging and release of dopamine and other monoamines. VMAT1 is primarily expressed in neuroendocrine cells; VMAT2 is primarily expressed in the central nervous system where it plays a major role in the modulation of monoamine release into the synaptic cleft. Drugs that inhibit VMAT2 have been shown to reduce the involuntary movements associated with dopaminergic receptor antagonists.

Methods: Valbenazine (NBI-98854, a novel VMAT2 inhibitor), its active metabolites (NBI-98782 or R,R,R-dihydrotetrabenazine [DHTBZ] and NBI-136110), and the other DHTBZ stereoisomers (S,R,R-, S,S,S-, R,S,S-) were examined in this study. Radioligand binding studies were conducted to evaluate the ability of valbenazine and its metabolites to inhibit binding of [3H]-DHTBZ and to inhibit uptake of monoamine substrates in cells expressing either human VMAT2 or VMAT1. Binding kinetics were also determined.

Results: Radioligand binding and direct kinetic studies showed that NBI-98782 inhibited [3H] DHTBZ binding in rat striatum (Ki=1.0-2.8 nM), rat forebrain (Ki=4.2 nM), and human platelet (Ki=2.6-3.3 nM) homogenates. Valbenazine and one additional metabolite (NBI-136110) were less potent inhibitors (197 nM and 220 nM, respectively) than NBI-98782. NBI-98782 is a potent inhibitor of VMAT2 with no effect on vesicular monoamnergic uptake in VMAT1-expressing cells.

Conclusions: In vitro findings indicate that NBI-98782, the primary metabolite of valbenazine, potently and selectively targets VMAT2 by binding and inhibiting vesicular monoaminergic uptake. The pharmacologic effects of this novel medication on monoamine transmission, particularly dopamine, is consistent with its reported clinical effects on tardive dyskinesia and other movement disorders.

Supported By: Neurocrine Biosciences, Inc.
Keywords: vesicular monoamine transporter 2 (VMAT2), dopamine, movement disorders

665. Valbenazine (NBI-98854) and Its Major Metabolites Specifically Modulate Neuronal Monoaminergic Function
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Background: Valbenazine and tetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors that share a common metabolite (NBI-98782 or R,R,R-dihydrotetrabenazine [DHTBZ]). By modulating the presynaptic packaging and release of dopamine, VMAT2 inhibitors may provide therapeutic benefits for various movement disorders.

Methods: Radioligand binding assays were conducted to assess in vitro affinities of valbenazine and tetrabenazine metabolites for VMAT2, including a broad screening panel testing for off-target binding (>80 targets). In vivo microdialysis was also performed to evaluate ability of NBI-98782 and tetrabenazine to modulate levels of dopamine, serotonin, and their metabolites in prefrontal cortex and striatum. In vivo function of tetrabenazine, valbenazine, and NBI-98782 in rats was determined using ptosis and prolactin release as surrogates for efficacy and adverse-effect, respectively.

Results: NBI-98782 exhibited high potency (Ki=4.2nM) and demonstrated higher selectivity than the other tetrabenazine metabolites (S,R,R-, S,S,S-, R,S,S-) at more than 80 targets. Microdialysis studies showed that both valbenazine and tetrabenazine significantly decreased the efflux of dopamine, norepinephrine, and serotonin. They also significantly increased the efflux of the dopamine metabolites (homovanillic acid, dihydroxyphenylacetic acid) and the serotonin metabolite (5-hydroxyindoleacetic acid) in the medial prefrontal cortex and dorsal striatum. Valbenazine, tetrabenazine, and NBI-98782 elicited ptosis in a dose-dependent manner, confirming VMAT2 activity. However, prolactin release was significantly lower with valbenazine and NBI-98782 compared to tetrabenazine.

Conclusions: Evidence from in vitro, in vivo, and microdialysis studies suggest that valbenazine and NBI-98782 selectively, specifically, and functionally inhibit VMAT2 without significant off-target activity. Valbenazine may be appropriate for treating hyperkinetic movement disorders such as Tardive Dyskinesia or Tourette syndrome.

Supported By: Neurocrine Biosciences, Inc.
Keywords: vesicular monoamine transporter 2 (VMAT2), dihydrotetrabenazine, movement disorders, microdialysis

666. VMAT2 Inhibition: A Novel Mechanism for Maintained Efficacy at Lowered Antipsychotic Doses
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Neurocrine Biosciences Inc

Background: The neuronal vesicular monoamine transporter-2 (VMAT2) is responsible for the packaging and ultimate release of monoamines into the synapse. NBI-98782 is the primary active metabolite of valbenazine with high affinity and selectivity for VMAT2. In conditions where antipsychotic treatment is indicated, concomitant use of valbenazine may offer the ability to use a lower dose of an antipsychotic while maintaining full efficacy.

Methods: Two well-established in vivo animal models were used to assess the effects of both independent and concomitant administration of NBI-98782 and the atypical antipsychotics risperidone and olanzapine on sensorimotor gating and antipsychotic-like behavior. Prepulse inhibition (PPI) evaluates sensorimotor gating while the conditioned avoidance task (CAR) was employed to evaluate potential effects...
antipsychotic efficacy directly related to dopaminergic neuromodulation.

Results: In vivo assessment of NBI-98782, risperidone, and olanzapine in PPI and CAR demonstrated that selective VMAT2 inhibition alone elicited efficacy comparable to that observed with atypical antipsychotics. Furthermore, combining subthreshold doses of NBI-98782 and an antipsychotic demonstrated maximal efficacy in CAR. Thus co-administration of NBI-98782 dose-dependently shifted the antipsychotic dose response to the left, indicating an increase in efficacy.

Conclusions: In vivo studies using classical models sensitive to both typical and atypical antipsychotics demonstrated that selective blockade of VMAT2 by NBI-98782 elicits an antipsychotic-like behavioral profile. Furthermore, full antipsychotic efficacy is maintained when subthreshold doses of both NBI-98782 and the antipsychotic are co-administered. These findings have important implications in clinical settings where first line or adjunct therapies include the use of typical or atypical antipsychotics known to have dose-related burden of adverse side-effects.

Supported By: Neurocrine Biosciences, Inc.

Keywords: vesicular monoamine transporter 2 (VMAT2), Dopamine, movement disorders, Sensorimotor gating, Neuromodulation

667. The in Vivo Electrophysiological Effects of Cariprazine on the Rat Midbrain Dopaminergic System

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Background: Schizophrenia symptoms may be associated with dysregulation of dopaminergic signaling. Cariprazine, a D3-prefering dopamine D3/D2 receptor partial agonist, is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. This study used in vivo electrophysiology to investigate the acute effects of cariprazine on dopamine neuron activity in rat brain.

Methods: Extracellular recordings of individual dopamine neurons in ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) were performed on anesthetized rats (n=5-10 per treatment group) receiving intravenous injections of cariprazine (cumulative doses to 80 µg/kg) and/or the D3 receptor antagonist SB-277,011-A (500 µg/kg), D2 receptor antagonist L741,626 (500 µg/kg), D3-prefering D3/D2 receptor agonist PD128,907 (10 µg/kg), and the non-selective dopamine receptor agonist, apomorphine (40 µg/kg).

Results: Cariprazine dose-dependently inhibited dopamine neuron firing by up to 38% in VTA (P<.01) and 46% in SNc (P<.001). Cariprazine prevented the PD128,907-induced suppression of neuron firing activity in the VTA, as did SB-277,011-A and L741,626 (P<.05). Cariprazine reversed apomorphine-induced suppression of neuronal firing in the SNc (P<.05). In both regions, L741,626, but not SB-277011A, inhibited cariprazine-induced suppression of dopamine neuron firing (VTA, P<.01; SNc, P<.0001).

Conclusions: Cariprazine behaved as a potent D3/D2 receptor partial agonist in the VTA and SNc, partially suppressing dopaminergic firing, but reversing dopamine receptor full agonist-induced firing inhibition. These effects were prevented by the D2 receptor antagonist, but not the D3 receptor antagonist, suggesting that D2 receptor activation was a major component contributing to these effects.

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Keywords: cariprazine, Dopamine, Schizophrenia, Electrophysiology


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Background: Schizophrenia symptoms may correlate with changes in cortical gamma oscillation power. Cariprazine, a potent D3/D2 receptor partial agonist with preferential binding to the D3 receptor, is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. This study investigated the effects of cariprazine on in vitro gamma oscillations.

Methods: Gamma oscillations were induced by acetylcholine/physostigmine in rat hippocampal slices (n=6-16 per condition) and extracellular field potentials recorded from area CA3b. Slices were treated with cariprazine, SB 277,011-A (D3 receptor antagonist), aripiprazole (D2 preferring D2/D3 receptor partial agonist), SV-156 (D2 receptor antagonist) and/or pramipexole (D3 receptor agonist). Desynchronization and resynchronization were also induced to assess the effects of cariprazine on oscillation dynamics.

Results: Pramipexole at 30 µM, but not 10 µM, significantly decreased stable gamma oscillation power and increased bandwidth and frequency (P<.05), while cariprazine, SB-277,011-A, SV-156, and aripiprazole had no effect. Cariprazine significantly potentiated the effect of 10 µM pramipexole on these parameters, but antagonized the effects of 30 µM pramipexole. Cariprazine also significantly decreased the bandwidth of induced unstable gamma oscillations (P<.05) and, in the dynamic oscillation model, significantly accelerated bandwidth normalization during resynchronization.

Conclusions: Cariprazine increased the periodicity of in vitro hippocampal gamma oscillations and acted as a D3 receptor partial agonist to augment effects of low receptor activation and antagonize those of high receptor activation. Cariprazine
modulated the speed of network oscillation resynchronization and normalization of unstable gamma oscillations, which may contribute to improvements in schizophrenia symptoms.

**Supported By**: Forest Research Institute, Inc., an Allergan affiliate, and Gedeon Richter Plc.

**Keywords**: cariprazine, Dopamine, Schizophrenia, Gamma oscillation

669. GPR52 Agonists Represent a Novel Approach to Treat Cognitive Deficits Associated with Schizophrenia

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**Background**: GPR52 is an orphan GPCR expressed primarily in the brain. Whereas in the striatum it is co-expressed almost exclusively in neurons with D2 dopamine receptors, in the cortex it mainly co-expresses with D1 dopamine receptors on glutamatergic neurons. Since GPR52 is G-s coupled, GPR52 agonists are hypothesized to show anti-psychotic as well as pro-cognitive activity due to their action in the striatum and cortex, respectively, making GPR52 an interesting target for the treatment of schizophrenia.

**Methods**: Compound potency was assessed by cAMP measurements from CHO cells overexpressing GPR52. To test GPR52 agonist influence cortical synaptic transmission, prefrontal cortical rat slices were stimulated in layer II and recorded in layer V. To demonstrate the GPR52 specificity of this stimulation, a GPR52 inverse agonist was used to block this effect. A social recognition task was used to assess if a GPR52 agonist showed pro-cognitive efficacy.

**Results**: The tool GPR52 agonist assessed in these tasks has an EC50 of 6 nM and showed concentration dependent synaptic potentiation in the cortical slices. This potentiation was blocked by a GPR52 inverse agonist, demonstrating that this effect is specifically mediated by GPR52. Rats receiving the compound demonstrated a significant reduction of interaction time in the social recognition task after a 24 h interval, suggesting that the compound acts in a pro-cognitive manner.

**Conclusions**: Taken together, these data show that GPR52 agonists potentiate synaptic transmission and show pro-cognitive effects. These data therefore underscore that GPR52 agonists have potential for treatment of cognitive symptoms in schizophrenia.

**Keywords**: GPR52, cognition, chemical potentiation

670. Heart Rate Variability Responses to a Standardized Virtual Reality Exposure in Veterans with PTSD

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**Background**: Virtual reality (VR) is growing in popularity for the treatment of posttraumatic stress disorder (PTSD). Psychophysiological data might be an objective indicator of treatment effectiveness. This study examines the HRV response to a series of combat-related VR events as well as non-combat stimuli of increasing complexity in individuals with and without PTSD.

**Methods**: OEF / OIF Combat Veterans (n = 19 with PTSD, n = 25 controls) were recruited from the Providence, RI VA. Exclusion criteria: abnormal electrocardiogram, benzodiazepines, beta blockers and alpha-2 agonists. VR content (visual, auditory, haptic, olfactory) increased in intensity throughout six 1-minute scenes with a 2-minute inter-stimulus interval in combat scenes; classroom scenes increased in complexity in a similar fashion. Short epoch heart rate variability (HRV) was continuously acquired throughout the VR trial. Data were analyzed using repeated measures ANOVA grouped by PTSD diagnosis and HRV indexed as the standard deviation between R-R intervals (SDRR).

**Results**: PTSD participants had higher SDRR vs. controls for combat graded VR (p < .0001). Within subject effects were not significant for classroom or combat VR scenes (p > .05). The within subject SDRR x PTSD interaction was non-significant for combat (p = .14) or classroom (p = .66) scenes.

**Conclusions**: Even with short epochs there is a detectable difference in HRV. HRV assessments typically require an epoch longer than 1-minute to reflect changes in autonomic regulation and therefore these data support further studies designed to assess HRV responses to VR stimuli in PTSD.

**Keywords**: Heart rate variability, PTSD - Posttraumatic Stress Disorder, Virtual Reality, combat stress, anxiety, sleep, exposure therapy, extinction, psychophysiology

671. Longitudinal Covariance of Resting State Heart Rate Variability and Borderline Personality Disorder Symptoms in Adolescents with Non-Suicidal Self-Injury

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**Background**: Resting state high-frequency heart rate variability (HF-HRV) – a potential trait marker of emotion regulation capacity – is reduced in borderline personality disorder (BPD). In adolescents with non-suicidal self-injury (NSSI), HF-HRV is inversely correlated with BPD symptoms. The study aimed to investigate if longitudinal changes in BPD symptoms are associated with changes in HF-HRV in adolescents with NSSI over time.

**Methods**: HF-HRV was recorded in female adolescents with NSSI (n = 17) according to DSM-5 section 3 diagnostic criteria...
who completed a baseline assessment and a one-year follow-up. Physiological data, structured clinical interviews and self-reports on psychopathological distress were obtained at both time points. Covariance and predictors of change in clinical outcomes and HF-HRV were assessed.

**Results:** Patients showed clinical improvements indicated by a reduction of depressive symptoms (z(34;17) = −3.74, p < .001), NSSI frequency (z(34;17) = −3.79, p < .001), and increases in the level of functioning (z(34;17) = 2.87, p = .004). No significant differences were observed on resting state HF-HRV (z(34;17) = −0.94, p = .348) recorded at baseline and follow-up. Changes in BPD symptoms were significantly associated with changes in resting HF-HRV (r(17) = −.516, p = .033).

**Conclusions:** Longitudinal changes in BPD symptomatology in adolescents engaging in NSSI are associated with changes in resting state HF-HRV, which gives support to HF-HRV as a trait marker of emotion regulation capacity. Results bear promise with respect to the implementation of measures of HF-HRV in the monitoring of patients and outcome assessment within psychiatric research. Future clinical studies are necessary to investigate the utility of HF-HRV to track treatment outcome in adolescents with BPD.

**Keywords:** Non-suicidal self-injury, Borderline Personality Disorder, Adolescents, Heart rate variability, longitudinal

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**672. Neural Mechanisms Underlying the Cognitive Regulation of Value Attribution: Abstraction of Contextual Information in the Monkey Hippocampus**

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**Background:** Human and animal studies have pointed to valence systems (reward valuation, reward prediction error) and to cognitive constructs such as working memory and cognitive control as potentially malfunctioning in several psychiatric disorders characterized by difficulties with emotional regulation. Animal studies have shown encoding of both valences at cellular level coexisting with the encoding of cognitive constructs. The purpose of this study is to investigate the modulatory mechanisms of cognitive constructs on reward valuation.

**Methods:** Two rhesus monkeys were trained to perform an action in response to visual cues. The monkey had to release a lever in response to two of four fractals and hold it in response to the other two. After a random number of trials, the contingency reverses, leading to a change in the rule in effect. Importantly, the reversals were not cued. Single cell activity electrophysiological recordings were collected from the anterior cingulate gyrus (ACC), hippocampus (HPC) and dorsolateral prefrontal cortex (DLPFC).

**Results:** Monkeys were able to infer the change in contingencies shortly after the first mistake following the reversal. Single neuron activity showed a strong encoding of the rule in effect in several brain regions, particularly the ACC and the HPC. Further analysis showed that the hippocampus relies more than other brain areas on a process of abstraction rather than memory recall.

**Conclusions:** Understanding the mechanisms of value attribution and cognitive control may elucidate individual differences leading to emotional dysregulation. Here we investigated some of the nodes belonging to a wider network.

**Supported By:** NARSAD, T32 fellowship, APA Research Fellowship

**Keywords:** Electrophysiological Single Unit Recordings, ACC, value, Hippocampus, Rhesus Monkey

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**673. Sleep Components in Early Postpartum Predict Later Postpartum Depression**

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**Background:** Postpartum depression (PPD) occurs in 15-20% of mothers worldwide and is associated with adverse outcomes for both mother and child. Prior research has established a relationship between overall sleep quality and PPD, but few studies have considered individual sleep components. We conducted an exploratory study in 62 mood-disordered women to consider the relationship between sleep components measured in the 3rd trimester and one month postpartum and the later development of PPD.

**Methods:** We measured sleep (Pittsburgh Sleep Quality Index (PSQI), subscale and total scores) and depressive symptoms (Inventory of Depressive Symptoms, Self-Report (IDS-SR)) in the third trimester and at one month and three months postpartum. We used bivariate and multivariate linear regression models to study the association between PSQI and IDS-SR scores, with adjustments for age, education, diagnosis, history of child abuse, antidepressant use, and depression.

**Results:** Higher global PSQI scores (reflecting poor sleep quality) as well as higher component scores for subjective sleep quality, sleep latency, sleep efficiency, sleep medication usage, and daytime dysfunction, measured at one month postpartum, were associated with increased IDS-SR scores (reflecting more severe depression) at three months postpartum (p = 0.003, 0.01, 0.01, 0.003, <.001, respectively). We did not find an association between poor sleep quality in the third trimester and PPD at one or three months.

**Conclusions:** Poor sleep quality in the early postpartum independently predicts development of later PPD. Targeting individual components such as sleep latency and efficiency may be an important postpartum therapeutic tool.

**Supported By:** NIMH K23MH074799 (Payne, PI)

**Keywords:** Postpartum Depression, Sleep, Mood disorder, Pregnancy

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**674. Subcallosal Cingulate Local Field Potential (SCC-LFP) 1/f Noise Changes during SCC Deep Brain Stimulation (DBS) for Major Depressive Disorder (MDD): Observations across Treatment Phases and Circadian Cycles**

Ashan Veerakumar, Vineet Tiruvadi, Bryan Howell, Allison Waters, Andrea Crowell, Patricio Riva Posse

**Background:** The subcallosal cingulate (SCC) is an important brain region for the treatment of major depressive disorder (MDD). Deep brain stimulation (DBS) of the SCC has been associated with increased interregional connectivity, however, the mechanisms of action of SCC DBS for MDD are not well understood. Here, we investigated the dynamics of SCC LFP 1/f noise during SCC DBS for MDD.

**Methods:** A total of 8 MDD patients underwent chronic SCC DBS with implanted electrodes bilaterally. LFP recordings were obtained in the SCC and the subcallosal corona radiata during SCC DBS. 1/f noise analysis was performed to quantify noise changes during SCC DBS.

**Results:** We observed significant 1/f noise changes in the SCC and the subcallosal corona radiata during SCC DBS. The 1/f noise changes were associated with changes in clinical outcomes and predicted treatment response.

**Conclusions:** Our results suggest that 1/f noise changes in the SCC and the subcallosal corona radiata during SCC DBS predict treatment response for MDD. Further studies are needed to elucidate the mechanisms of action of SCC DBS for MDD.
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**Background:** SCC-DBS is an emerging intervention for treatment-resistant MDD, with recent innovations to improve targeting by image-guidance. But subsequent to implantation, no biomarkers exist to guide treatment, leaving room for avoidable adverse events and battery replacements. Utilizing SCC-LFP data during a course of therapeutic SCC-DBS, we reproduce known circadian LFP frequency domain 1/f slope changes, and introduce 1/f shifts observed during phases of treatment.

**Methods:** N=6 patients were implanted with an investigational neurostimulator/recorder with informed consent and institutional approval. SCC-LFP recordings with stimulation off were collected from a 1month post-implantation resting phase, weekly during a 6month treatment phase, and from a 1week single-blinded discontinuation experiment. 1/f slope was quantified on Welch periodograms of 15sec epochs using simple linear regression. Comparative statistics include a general linear model (GLM) to compare across treatment phase, and a paired t-test for sleep-wake comparisons. 5/6 patients who responded by 6months were included in this analysis.

**Results:** As reported in previous human and animal studies, we observe a significant increase in the 1/f slope magnitude during sleeping hours. As supported by the GLM, the 1/f slope in the left electrode undergoes a decrease in magnitude with stimulation and a mild increase during the 1week discontinuation experiment, notably not reaching the pre-stimulation and a mild increase during the 1week treatment baseline. Reproduction of circadian 1/f changes demonstrates the ability of SCC-LFP’s to detect large shifts in brain state. 1/f changes across treatment phase, while less pronounced, and observed in a small sample size, suggest that SCC-DBS stably, and potentially therapeutically, increases the randomness of SCC neural activity.

**Keywords:** Deep Brain Stimulation, Major Depressive Disorder (MDD), Electrophysiology

675. Nuclear Factor-κB Activation Contributes to Vascular Endothelial Dysfunction in Adults with Major Depressive Disorder

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**Background:** Major Depressive Disorder (MDD) is associated with chronic low-grade inflammation. In rodent models of depression, inflammation contributes to vascular dysfunction via reductions in nitric oxide (NO) bioavailability. However, the influence of inflammation on endothelial function in adults with MDD remains unexplored. We hypothesized that increases in nuclear factor-κB (NF-κB) activity contribute to MDD-induced endothelial dysfunction.

**Methods:** Six otherwise healthy adults (3 men; 21±1yrs) with MDD (PROMIS score 26.7±1.8) participated. Red blood cell flux (laser Doppler flowmetry) was measured during graded intradural microdialysis perfusion of acetylcholine alone (ACh; 10-10-1-1M) and during co-perfusion with the NO synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME; 20mM) pre- and post-treatment with the NF-κB inhibitor salsalate (nonacetylated salicylate, 4 days x 3000-4500mg). Endothelium-independent vasodilation was assessed via perfusion of sodium nitroprusside (SNP; 10-7-10-1M), Cutaneous vascular conductance (CVC=flux•mmHg-1) was expressed as a percentage of maximum. Differences in ACh-induced vasodilation between treatment and microdialysis perfusate were analyzed by two-way repeated-measures ANOVA.

**Results:** Salsalate treatment increased plasma salicylate concentrations to the mid-therapeutic range (20.8±1.1) and improved endothelium-dependent vasodilation (Pre: 67±7 vs. Post: 87±8%CVCmax; P=0.01). Inhibition of NO synthase had no effect on ACh-induced vasodilation pre-salsalate (ACh: 67±7 vs. ACh+L-NAME: 64±5%CVCmax; P=0.59) but attenuated ACh-induced vasodilation post-salsalate (ACh: 87±8 vs. ACh+L-NAME: 52±3%CVCmax; P≤0.01). SNP-induced vasodilation was not different pre- and post-treatment (Pre: 89±2 vs. Post: 92±5%CVCmax; P=0.60).

**Conclusions:** These preliminary data provide the first direct evidence that systemic inflammation, specifically NF-κB activation, reduces vascular NO bioavailability, thus contributing to endothelial dysfunction in otherwise healthy adults with MDD.

**Supported By:** American Heart Association

**Keywords:** Endothelium-dependent dilation, Inflammation, Nitric Oxide, Major Depression, Vascular dysfunction

676. Gut Microbiota Distributions Predict Mood Disorder Symptoms and Mediate Dietary Interactions

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**Background:** The gut microbiota are key modulators of the gut-brain axis, which directly links the peripheral gut to the brain. Integrating the gut microbiota into the biological model of mood dysfunction may help determine biological variables associated with psychiatric illness.

**Methods:** Bacterial distribution of depressed participants (both anxious [n=9] and melancholic presentation [n=5]) and healthy controls (n=4) were quantified using bacterial group qPCR and then compared to symptoms obtained by psychiatric assessments (including the Quick Inventory of Depressive Symptomatology – Self Report [QIDS-SR] and the Generalized Anxiety Disorder 7-item [GAD-7]) and a
Conclusions: Our findings suggest that patients with schizophrenia demonstrate abnormalities in the processing of somatosensory information. These results may help to develop a model of somatosensory dysfunction in schizophrenia that can be used to direct treatments for somatosensory related cognitive deficits (e.g., auditory hallucinations). These treatments may ultimately lead to improved symptoms in this disorder.

Supported By: NARSAD, CIHR
Keywords: somatosensory, Schizophrenia, peripheral nerve stimulus, EEG

678. Differential Effects of Cannabis versus Tobacco on Theta-Gamma Coupling in Schizophrenia

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Background: Co-morbid cannabis dependence in schizophrenia significantly exacerbates positive and negative symptoms; however effects on cognition are unclear. Tobacco, which is often co-administered with cannabis, may have beneficial effects on cognition. Impaired theta-gamma coupling in dorsolateral prefrontal cortex (DLPFC) has been hypothesized to underlie pervasive working memory deficits in this disorder. This study determined effects of cannabis and tobacco on coupling during working memory performance among 4 groups: cannabis+tobacco versus tobacco smoking patients with schizophrenia, compared to non-psychiatric controls.

Methods: 15 patients (mean age 30.9 ± 9.2 years) and 17 controls (mean age 28.4 ± 6.6 years) daily cannabis+tobacco smokers and 16 patients (mean age 39.7 ± 10.2) and 12 controls (mean age 39.8 ± 11.9 years) daily tobacco smokers performed the N-back (1 and 3) task. Coupling was measured from DLPFC for correct responses to targets using EEG.

Results: Patients performed significantly worse on N-Back task compared to controls (F=4.750; df=1,56; p=0.034). Significant diagnosis x working memory load (F=4.702; df=1,54; p=0.035) interaction indicative of reduced theta-gamma coupling among patients in the 3-Back compared to controls (t=-2.177; df=57; p=0.034). Theta-gamma coupling was significantly greater among cannabis+tobacco smokers compared to tobacco smokers (F=15.294; df=1,54; p<0.0001).

Conclusions: Findings demonstrate impaired theta-gamma coupling among patients with schizophrenia during working memory. However, concurrent cannabis combined with tobacco use may enhance coupling compared to tobacco smoking alone. These effects were selective to the target correct responses with no differences of theta-gamma coupling observed in the non-target correct responses.

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677. Evidence for Prefrontal Cortex Hypoexcitability in Schizophrenia through Somatosensory Evoked Potentials

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CAMH Toronto

Background: Many patients with schizophrenia exhibit a variety of symptoms relating to alterations in the somatosensory system. Little is known, however, about the neural substrates underlying somatosensory impairments in schizophrenia.

Methods: The median nerve was stimulated using a peripheral nerve stimulator in 30 healthy subjects (mean age 18.7) and 18 patients with schizophrenia (mean age 38.9, SD = 13.9). The peripheral nerve stimulus intensity was adjusted to 300 percent of sensory threshold and delivered at 0.1 Hz. Somatosensory evoked potentials (SSEPs) were acquired through EEG. We collected and averaged 100 trials; and the recording electrodes of interest were the C3/CP3 electrodes representing the motor cortex and the F7/F5 electrodes representing the DLPFC. A time window of [-50,250] ms was used for the analysis. ICA was used for mitigating signal artifact.

Results: Certain bacterial groups were correlated with mood disorder symptoms, with some associations being specific to one sub-type of depressive presentation or related to consumption of certain dietary items, including soda. For all participants including healthy controls, amount of total bacteria predicted trouble falling asleep (p = .049) and increased depressed mood scores on the QIDS-SR (p = .045), and reduced Enterobacteriaceae predicted an increased score on the feeling nervous/anxious item of the GAD-7 (p = .018). In those with melancholic depression, Lactobacillus/Enterococcus was positively associated with psychomotor agitation items on both the QIDS-SR and the GAD-7 (p = .019 and .047, respectively). A mediation model indicated that these bacteria significantly mediated a relationship between soda consumption and the psychomotor agitation as measured by the QIDS-SR (95% CI: −5.01, −3.75).

Conclusions: These data indicate important associations between bacterial groups and symptoms of depression and anxiety. Quantifications of peripheral immune response and integration into the model are being pursued.

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Keywords: Gut microbiota, Depressive symptoms, Anxiety, diet
Canadian Institute of Health Research (CIHR) Operating Grant MOP#115145 to Dr. George
**Keywords:** Cannabis use disorder, Tobacco, Schizophrenia, Theta-Gamma Coupling, Working memory

679. MicroRNA -19b Acts as a Sex-Dependent Regulatory Hub for PTSD and Chronic Widespread Pain Development following Trauma Exposure

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**Background:** PTSD and chronic widespread pain (CWP) are frequent co-morbid sequelae of trauma that occur at different rates in women and men. We sought to identify microRNA (miRNA) that may contribute to sex-dependent differences in vulnerability to these outcomes using in silico, human, molecular, and animal data.

**Methods:** Monte Carlo simulations identified miRNA in which predicted targeting of PTSD or CWP genes was most enriched (p<0.05). Expression of the miRNA most strongly predicted to target PTSD and CWP genes in these simulations, miR-19b, has been shown to be influenced by estrogen and stress exposure. We evaluated whether peritraumatic miR-19b blood expression predicted PTSD and CWP development in a cohort of individuals experiencing motor vehicle collision (MVC) (n=178), and whether miR-19b was sex-dependent in animal models of stress exposure.

**Results:** A sex-dependent relationship was observed between initial miR-19b levels and both PTSD development (miR-19b*sex interaction OR=1.41, p=0.039) and CWP development (miR-19b*sex interaction OR=1.46, p=0.031) 6 months following MVC. Sex-dependent expression of miR-19b was also observed in two animal models. The potential importance of miR-19b to PTSD/CWP pathogenesis is supported by further analyses indicating that: miR-19b targets are enriched in the circadian rhythm (CR) pathway, miR-19b expression is negatively correlated with key CR transcripts following MVC, such as CLOCK and RORA, and miR-19b directly binds CR targets in in vitro binding studies.

**Conclusions:** Together, these results highlight the sex-dependent expression of miR-19b and suggest that miR-19b plays a critical regulatory role in PTSD and CWP development following trauma/stress exposure.

**Supported By:** R01 AR060852

**Keywords:** microRNA, PTSD - Posttraumatic Stress Disorder, Chronic widespread pain, Sex differences, Circadian Rhythms

680. Lurasidone in Post-Menopausal Females with Major Depressive Disorder with Mixed Features: Post-Hoc Analysis of a Placebo-Controlled Trial

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1Worldwide Clinical Trials, 2Sunovion Pharmaceuticals

**Background:** Several studies have found depressed, post-menopausal females show a significantly poorer response than pre-menopausal females to the SSRI class of antidepressants. The atypical antipsychotic lurasidone, which has a different mechanism of action from SSRIs, was recently shown in a 6-week randomized, flexible-dose, placebo-controlled study (N=209), to be effective in treating major depressive disorder (MDD) with mixed features. This post-hoc analysis assessed efficacy of lurasidone by menopausal status.

**Methods:** The main outcome measure for this post-hoc analysis was change in MADRS score from baseline to week 6. Additional assessments included the CGI-S, HAM-A and YMRS. Lurasidone-treated women ages 52 years old and greater (presumptive post-menopausal, n=56) were compared on key outcome measures to those less than 52 years old (n=17) using a mixed model for repeated-measures analysis. An exploratory analysis was conducted removing presumptive peri-menopausal women (ages 45-51 years old) to allow for clearer definition of pre- and post-menopausal status.

**Results:** The post-menopausal and younger female groups were similar in demographic characteristics, history of major depressive episodes, baseline rating scores, and lurasidone study dose. Both analyses showed that lurasidone-treated post-menopausal and younger females responded significantly (p= 0.016 or less) compared to placebo on the MADRS, and that post-menopausal patients had a better response (2 points greater reduction) than younger patients. All other secondary outcome measures between lurasidone and placebo treatment were significant (p=0.045 or less) for both age groups.

**Conclusions:** In this post-hoc analysis lurasidone was effective in treating MDD with mixed features in both post-menopausal and younger female patients.

**Supported By:** Sunovion Pharmaceuticals Inc. The sponsor was involved in the study design, collection, and analysis of data. The interpretation of results and the decision to submit this manuscript for publication were made by the authors independently.

**Keywords:** lurasidone, female, Postmenopause, Major Depressive Disorder (MDD), Depression

681. Diagnosis of Schizotypal Personality Disorder, Sex-Gender and Age Effects on Neuropsychological Performance

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1Worldwide Clinical Trials, 2Sunovion Pharmaceuticals

**Background:** Several studies have found depressed, post-menopausal females show a significantly poorer response than pre-menopausal females to the SSRI class of antidepressants. The atypical antipsychotic lurasidone, which has a different mechanism of action from SSRIs, was recently shown in a 6-week randomized, flexible-dose, placebo-controlled study (N=209), to be effective in treating major depressive disorder (MDD) with mixed features. This post-hoc analysis assessed efficacy of lurasidone by menopausal status.

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**Results:** The post-menopausal and younger female groups were similar in demographic characteristics, history of major depressive episodes, baseline rating scores, and lurasidone study dose. Both analyses showed that lurasidone-treated post-menopausal and younger females responded significantly (p= 0.016 or less) compared to placebo on the MADRS, and that post-menopausal patients had a better response (2 points greater reduction) than younger patients. All other secondary outcome measures between lurasidone and placebo treatment were significant (p=0.045 or less) for both age groups.

**Conclusions:** In this post-hoc analysis lurasidone was effective in treating MDD with mixed features in both post-menopausal and younger female patients.

**Supported By:** Sunovion Pharmaceuticals Inc. The sponsor was involved in the study design, collection, and analysis of data. The interpretation of results and the decision to submit this manuscript for publication were made by the authors independently.

**Keywords:** lurasidone, female, Postmenopause, Major Depressive Disorder (MDD), Depression
Background: Although sex-gender studies in schizophrenia suggest milder cognitive impairment in women compared to men, comparable empirical evidence found in schizotypal personality disorder (SPD) is minimal and has yet to be fully delineated. Moreover, whereas age-related declines in attention and memory may be accelerated in schizophrenia, less is known about age-related neuropsychological functioning among men and women diagnosed with SPD.

Methods: This study investigates sex-gender differences in neuropsychological functioning in a large community sample (n=180) of healthy volunteers matched by age and sex with unmedicated men and women diagnosed with schizotypal personality disorder (SPD=82). All volunteers received structured-diagnostic interviews (SCID), standardized cognitive and neuropsychological assessments previously shown to reflect deficits in general intelligence (Wechsler Abbreviated Scales Intelligence, WASI), and attention (Trail-Making-Tasks) and memory (verbal, auditory and visual spatial) functioning in schizophrenia, and provided responses to demographic, symptomatic mood state (e.g. Beck Depression Inventory) and personality trait (Schizotypy Personality Questionnaire) questionnaires. Multivariate Analysis of Variance (MANOVA) was used to test for main effects of Diagnostic-group-by-sex interaction using continuous age as a covariate.

Results: On a task of visuospatial-perceptual reasoning results show a significant Diagnostic-group-by-Sex interaction effect; women with SPD showed more impairment than men with SPD. For all subsequent tasks, men and women with SPD performed equally poorly compared with HVs.

Conclusions: Overall, results indicate that compared with schizophrenia, sex differences in intellectual ability, and attention and memory performance are not preserved in SPD women.

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Keywords: Schizotypal Personality Disorder, Attention, Memory, Sex differences, Neuropsychology

682. Estrous Cycle-Dependent Alterations in Cocaine Affinity at the Dopamine Transporter Underlie Enhanced Cocaine Reward in Females

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1Icahn School of Medicine at Mount Sinai, 2Stanford University

Background: While both males and females become addicted to cocaine, females transition to dependence faster, take more cocaine, and experience greater difficulty remaining abstinent. Here, we define a sex-specific neural mechanism contributing to this enhanced cocaine reward in females.

Methods: Using electrophysiology of ventral tegmental area (VTA) dopamine neurons and fast scan cyclic voltammetry in the nucleus accumbens (NAc), in vivo calcium imaging and conditioned place preference, we recorded pathway specific VTA and NAc responses to cocaine-associated contextual cues in male mice and in intact females over the estrous cycle. Using designer receptors exclusively activated by designer drugs (DREADDs) we directly linked downstream alterations in dopamine transporter function to activity dependent changes at the level of the VTA.

Results: We identified an estrous-cycle dependent enhancement of dopaminergic function in both the VTA and NAc. This enhancement is converged with an increased ability of cocaine to bind directly to the dopamine transporter and augment dopamine levels during estrus. Using DREADD-induced activation of VTA dopamine neurons to enhance firing we were able to mimic the effects of estrous cycle on the dopamine system and subsequent reward processing in both diestrus females and males. These changes lead to not only enhanced reward processing during estrus, but potent and long-lasting associations between cocaine and associated environmental cues that extend to other stages of the estrous cycle.

Conclusions: Together we define a basic mechanism by which estrous cycle dependent changes in the dopamine transporter underlies susceptibility to cocaine addiction by promoting persistent cue-reward associations that can precipitate relapse.

Supported By: National Institute on Drug Abuse (E.J.N., R01 DA14133), (E.S.C. K99 DA042111); The Brain and Behavior Research Foundation (NARSAD, E.S.C.); National Institute of Mental Health (E.J.N., R01 MH51399, P50 MH096890) and National Institute of Alcoholism and Alcohol Abuse (M.H.H. R01 AA022445; B.J. F31 AA022862).

Keywords: Dopamine transporter, calcium imaging, Ventral Tegmental Area, cocaine addiction, Reward Learning

Late Breaking Poster Session

The Late Breaking poster abstracts were accepted after this supplement was published. See the On-Line Program Planner or Mobile App for the complete abstract.
Saturday, May 20, 2017

PLENARY SESSION
Microcircuits, Math and Mental Health - Dissecting Complexity
Saturday, May 20, 2017 - 8:00 AM - 11:30 AM
Sapphire AN
Chair: Paul Holtzheimer

Saturday Abstracts

683. Tools for Mapping and Controlling Brain Circuits: Optogenetics and Expansion Microscopy
Edwin Boyden
Massachusetts Institute of Technology, Cambridge, Massachusetts

To enable the understanding and repair of complex biological systems such as the brain, we are creating novel optical tools that enable molecular-resolution maps of large scale systems, as well as technologies for observing and controlling high-speed physiological dynamics in such systems. First, we have developed a method for imaging large 3-D specimens with nanoscale precision, by embedding them in a swellable polymer, homogenizing their mechanical properties, and exposing them to water – which causes them to expand isotropically severalfold. This method, which we call expansion microscopy (ExM), enables scalable, inexpensive diffraction-limited microscopes to do large-volume nanoscopy (Chen et al. 2015; Chen et al. 2016; Tillberg et al. 2016). Second, we have developed a set of genetically-encoded reagents, known as optogenetic tools, that when expressed in specific neurons, enable their electrical activities to be precisely driven or silenced in response to millisecond timescale pulses of light; these tools are starting to reach their physical limits of performance (Chuong et al., 2014; Klapoetke et al., 2014). Finally, we have collaboratively developed strategies to image and record fast physiological processes in 3-D with millisecond precision, and are using them to acquire neural activity maps with single cell resolution in living brain circuits. In this way we aim to enable the systematic mapping, control, and dynamical observation of complex biological systems like the brain.

References

684. Multimodal Imaging, Neural Circuits and Mood Disorders
Mary Phillips
University of Pittsburgh, Pittsburgh, Pennsylvania

My research uses multimodal neuroimaging to examine patterns of functional and structural abnormalities in emotion regulation neural circuitry in mood disorders across youth and adulthood (1, 2). The overarching aim of this research is to increase understanding of the neural circuitry underlying mood disorders to: 1) identify neural biomarkers to aid diagnosis; 2) identify objective markers of risk for future development of these disorders in youth and young adults; and 3) identify neural targets that may play an important role in the discovery of new and more effective treatments for mood and anxiety disorders. My presentation will focus on the use of multimodal neuroimaging techniques to elucidate functional and structural abnormalities in reward processing and emotional regulation circuitries that are associated with dimensions of reward-related psychopathology in youth and adults. I will focus in particular on recent studies in my laboratory that have used these techniques to elucidate the neural bases of impulsivity and sensation seeking in youth and young adults, and links between these underlying neural mechanisms and predisposition to risky decision making and behaviors. I will also present data from our studies in at-risk youth that have identified neurodevelopmental abnormalities in reward and emotional regulation circuitries that are associated with worsening affective pathology (3, 4), and studies that have identified neural biomarkers reflecting underlying pathophysiological processes that predict development of aberrant, impulsive sensation seeking-related behaviors in these youth (5). Finally, I will present findings from ongoing studies in my laboratory that seek to determine the extent to which novel neuromodulation interventions, including transcranial direct current stimulation, targeted on specific neural biomarkers of impulse sensation seeking in young-mid-life adults can ameliorate abnormalities in reward and emotional regulation neural circuitries and, in turn, reduce propensity for risky decision making and behaviors and future affective pathology.

Saturday Abstracts

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Edwin Boyden
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To enable the understanding and repair of complex biological systems such as the brain, we are creating novel optical tools that enable molecular-resolution maps of large scale systems, as well as technologies for observing and controlling high-speed physiological dynamics in such systems. First, we have developed a method for imaging large 3-D specimens with nanoscale precision, by embedding them in a swellable polymer, homogenizing their mechanical properties, and exposing them to water – which causes them to expand isotropically severalfold. This method, which we call expansion microscopy (ExM), enables scalable, inexpensive diffraction-limited microscopes to do large-volume nanoscopy (Chen et al. 2015; Chen et al. 2016; Tillberg et al. 2016). Second, we have developed a set of genetically-encoded reagents, known as optogenetic tools, that when expressed in specific neurons, enable their electrical activities to be precisely driven or silenced in response to millisecond timescale pulses of light; these tools are starting to reach their physical limits of performance (Chuong et al., 2014; Klapoetke et al., 2014). Finally, we have collaboratively developed strategies to image and record fast physiological processes in 3-D with millisecond precision, and are using them to acquire neural activity maps with single cell resolution in living brain circuits. In this way we aim to enable the systematic mapping, control, and dynamical observation of complex biological systems like the brain.

References
685. On Being a Circuit Psychiatrist
Joshua Gordon
Columbia University, New York, New York

Recent technological advancements in the study of neural circuits provide reasons to be optimistic that novel treatments for psychiatric illnesses are just around the corner. Maximizing the chances of translating these advancements into real improvements in patient care requires a carefully considered road map. I will discuss my own work dissecting the circuitry function and white matter structure in youth. Neurology Psychiatry. 2016 Feb 23. doi: 10.1038/mp.2016.5.

686. A Data-Driven Method for Deriving Shorter DSM Symptom Criteria Sets: The Case for Alcohol Use Disorder
Melanie Wall
Columbia University, New York, New York

With the release of the DSM-5, sponsors describe the new guide as a ‘living document’ hoping to break the lengthy revision process of its predecessors. Under a new continuous improvement model, the APA has established a new DSM web portal (www.dsm5.org) to field proposed changes (First, 2016). One possible improvement could come from shortening lengthy criteria sets. The DSM-5 provides a fixed-length set of 11 criteria associated with Alcohol Use Disorder (AUD) combining Alcohol Dependence and Alcohol Abuse from DSM-IV (Hasin et al. 2013). The goal of the present study is to develop a method to systematically identify subsets of the 11 criteria and associated cut-off rules that will yield diagnosis as similar as possible to using all 11 criteria. We do this by: (1) maximizing the association between the sum scores of all 11 criteria with newly constructed subscales from subsets of criteria, (2) optimizing the similarity of AUD prevalence between the current DSM-5 rule and newly constructed diagnostic short-forms, (3) maximizing sensitivity and specificity of the newly constructed diagnostic short-forms against the current DSM-5 rule, and (4) minimizing any differences in the accuracy of the short-form across chosen covariates (i.e. age, sex, race, psychiatric comorbidity). In our application to DSM-5 AUD, there were more than 11,000 possible diagnostic short-forms that could be created and using our method we were able to narrow the optimal choices down to 16. Results found that “Neglecting Major Roles” and “Activities Given Up” could be dropped from the criteria set with practically no change in terms of who is diagnosed. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) was used as the data source.

References

687. Mechanistic Studies in Primates Implicating Altered Amygdala CRH Systems in Pathological Anxiety
Ned Kalin
University of WI School of Medicine and Public Health

Background: Nonhuman primates provide unique and important translational models of psychopathology. We established viral vector gene expression strategies in rhesus monkeys to examine molecular alterations in the central nucleus of the amygdala (Ce) that contribute to pathological anxiety. Understanding the effects of CRH in this region in primates is particularly relevant to humans as primate species differ from rodents in the expression of CRH1 and CRH2 receptors.

Methods: Extensive anxiety phenotyping, along with multimodal neuroimaging, was used to assess effects of over expression of CRH in the rhesus monkey central nucleus of the amygdala.
Intraoperative real-time MRI was used to selectively infect the Ce with an AAV5 vector over expressing the CRH gene.

**Results:** Results demonstrated that over expression of CRH in the Ce resulted in increased measures of anxiety including increases in anxious temperament. In addition, FDG-PET scanning revealed that over expression of CRH resulted in increased metabolism in the neural circuit that underlies anxiety including the dorsal amygdala and the posterior orbital frontal cortex. Chronic over expression of CRH also led to other functional and structural brain changes.

**Conclusions:** These studies are highly relevant as there are important differences in the regional expression of CRH receptor subtypes between rodent and primate species. These are the first data manipulating the CRH gene in primates to demonstrate a potential role of this system in mediating pathological anxiety. These studies suggest the importance of the CRH system in the central nucleus of the amygdala in mediating human stress-related psychopathology.

**Supported By:** NIH

**Keywords:** Anxiety, monkey, CRH, imaging, amygdala

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**689. Mifepristone Plasma Levels, Receptor Blockade and Clinical Response in Patients with Psychotic Depression**

**Joseph Belanoff**

Corcept Therapeutics

**Background:** Psychotic Depression (PD) is a severe form of depression characterized by hypothalamic-pituitary-adrenal (HPA) axis overactivity and high morbidity and mortality. No treatment for it has been approved by the FDA. Because it modulates cortisol’s activity, mifepristone has been studied in over 1,400 patients with PD to test its ability to rapidly reduce psychotic symptoms. Receiver Operator Curve (ROC) analyses have been performed on mifepristone trough plasma level data in these studies to identify optimal values discriminating responders from non-responders. We present data on relationships among plasma drug, degree of cortisol modulation (as illustrated by changes in cortisol and ACTH levels) and clinical response.

**Methods:** Data were collected across 5 phase II/III PD studies (1400 patients) treated for 7 days with mifepristone (300-1,200mg per day) or placebo, followed for an additional 7 weeks. Morning cortisol levels were assessed before and after 7 days of treatment. Trough drug plasma levels were drawn prior to the final dose of study drug. Response was defined as a 50% reduction in psychotic symptoms from baseline to study day 7 sustained to day 56.

**Results:** Patients with high mifepristone plasma level patients demonstrated significantly higher response rates than patients with low mifepristone plasma level or patients who received placebo. In addition, patients with high plasma drug levels demonstrated significantly greater increases in ACTH and cortisol levels than did the other two groups.

**Conclusions:** Mifepristone at higher drug plasma levels has significantly antipsychotic and biological effects in PD patients. Administration of mifepristone was safe and well tolerated.

**Supported By:** Corcept Therapeutics

**Keywords:** Mifepristone, Psychotic Depression

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**690. Novel Therapeutics in PTSD: A Randomized Clinical Trial of Mifepristone**

**Julia Golier¹**, Julia Golier², Robin Hurley³, Rachel Yehuda², Dewleen Baker⁴, Xue Li⁵, Brendan W. Bechard⁶, Lisa Robin⁷, Janine Flory⁸, Timothy Kimbrell⁷, Marcel Blizien⁹, and Domenic Reda²

¹Mt. Sinai School of Medicine, ²Mount Sinai School of Medicine, James J. Peters VAMC, ³Wake Forest School of Medicine, MIRECC, VAMC, ⁴San Diego Veterans Affairs, ⁵VA Cooperative Studies Program Coordinating Center, ⁶James J. Peters VAMC, ⁷Central Arkansas Veterans Healthcare System, University of Arkansas, ⁸VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center

**Background:** PTSD is a debilitating illness for which few effective pharmacological treatments exist. Given ample evidence of dysregulation of the hypothalamic pituitary
adrenal (HPA) axis in PTSD, including enhanced glucocorticoid receptor sensitivity, we assessed the efficacy and safety of mifepristone, a type II glucocorticoid receptor antagonist, in the treatment of PTSD.

Methods: A multi-center phase IIa, double-blind, randomized clinical trial of mifepristone versus placebo was conducted through the Department of Veterans Affairs. Eighty-one male veterans were randomized to treatment with either mifepristone (600 mg/day) or placebo for seven days followed by periodic assessments over three months. Statistical selection theory will be used to determine if there is a signal for the efficacy of mifepristone on clinical response, based on reduction in the total score of the Clinician Administered PTSD Scale (CAPS).

Results: Preliminary results will be presented to show the proportion of clinical responders (defined as a 30% or greater reduction in CAPS total score from baseline) at one month posttreatment on mifepristone vs. placebo. Information will also be provided about the sustainability of response and adverse events.

Conclusions: This study will inform us as to whether there is a sufficient signal to warrant a larger scale trial of mifepristone in PTSD. If short-term mifepristone treatment is found to be effective and safe it would represent a novel approach to pharmacological treatment that is very different from chronic psychotropic medication usage and open up additional avenues for therapeutic manipulation of neuroendocrine activity in PTSD.

Supported By: Department of Veterans Affairs, Cooperative Clinical Trial Award Program (#0004).

Keywords: Glucocorticoids, PTSD - Posttraumatic Stress Disorder, Clinical Trials, Hydrocortisone, Mifepristone

691. RNA-sequencing of the Subgenual Anterior Cingulate Cortex in Adult Major Psychiatric Disorders

Nirmala Akula1, Robin Kramer2, Qing Xu1, Kory Johnson2, Stefano Marenco1, Jose Apud1, Harker Rhodes1, Brent Harris1, Barbara Lipska3, and Francis McMahon1

1National Institute of Mental Health, 2NINDS, 3NIH/NIMH

Background: The subgenual anterior cingulate cortex (ACSG) has been implicated in both mood disorders and schizophrenia, but gene expression in this brain region has been little studied. Here we report the first large-scale study of the ACSG transcriptome in major psychiatric disorders.

Methods: A total of 200 ACSG samples (39 bipolar disorder (BD), 54 major depression (MDD), 46 schizophrenia, 61 controls) were dissected from brains collected at the NIMH-HBCC. Stranded, paired-end sequencing of high quality RNA (RIN 6) was performed on the Illumina HiSeq 2500. The resulting 125bp reads were mapped to the reference genome (hg38) using TopHat v2.1.1. Gene-level analyses were performed using HTSeq and DESeq2 was used for quality control, normalization, and differential gene expression, with correction for known covariates.

Results: Of the 21 billion total reads obtained, 98M reads mapped to the reference genome and 70M reads were properly paired, per sample. A total of 38 genes, 68 genes and 141 genes were differentially expressed (FDR<10%) in BD, MDD and schizophrenia, respectively. The overlap of differentially expressed genes across disorders was highly significant (hypergeometric p-value<1.9E-05). Two genes, NR4A1(NUR77) and NR4A2(NURR1), were differentially expressed in all 3 disorders. Pathway enrichment analysis implicated the MHC class II.

Conclusions: To our knowledge this is the largest study of the ACSG transcriptome in postmortem brain. The cross-disorder overlap in gene expression recapitulates genome-wide association study results and highlights the shared genetic architecture among major psychiatric disorders. Future analyses will examine transcript-level expression and gene co-expression networks.

Supported By: 1-ZIC-MH002903-09

Keywords: Anterior cingulate cortex, RNA sequencing, Bipolar disorder, Schizophrenia, Major depression

692. From Nucleosome to Nucleus: 3D Genome Mappings in Mouse Models of Psychiatric Disease, and in Human Postmortem Brain

Schahram Akbarian, Prashanth Rajaran, and Kristen Brennand

Icahn School of Medicine at Mount Sinai

Background: Non-random chromosomal conformations, including promoter-enhancer loopings bypassing kilo- or megabases of linear genome, provide a critical layer of transcriptional regulation, and mobilize vast amounts of non-coding sequence into physical proximity of genes important for neurodevelopment, cognition and behavior. Loop-bound intergenic and intronic non-coding sequences have been implicated in psychiatric and adult-onset neurodegenerative disease, but insight into the developmental and disease-associated changes in the regulation of the neuronal and non-neuronal ‘3D genome’, including its inter-relation with histone modification landscapes and other layers of epigenetic regulation, has been limited.

Methods: Genome-scale restriction digest-religation assays in intact nuclei from human and mouse brain and neural cultures derived from pluripotent stem cells (in situ Hi-C). Chromatin immunoprecipitation followed by next generation sequencing from specific subtypes of neurons and glia, and RNA-seq transcriptome sequencing.

Results: A significant subset of chromosomal loop formations and chromosomal interaction domains are differentially regulated in neural precursors compared to differentiated neurons and glia. A subset of risk haplotypes (Psychiatric Genomics Consortium) locate to such types of
cell-specific chromosomal loopings associated with differential levels of gene expression. Histone methyltransferase mutant mice show disruption of long-range, megabase scale of chromosomal loopings that show an unexpected specificity for a subset of topologically associated domains (TADs).

**Conclusions:** Comprehensive mapping of the 3D genome across normal and diseased human and mouse brain development is expected to provide novel insights into the neurobiology and (epi)genetic risk architectures of psychiatric disease.

**Supported By:** NIH R01MH106056

**Keywords:** in situ Hi-C, epigenome, 3D genome, chromosomal conformation, postmortem

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**693. Identification, Regulation and Characterisation of Transcribed Intergenic Regions in Human Substantia Nigra and Putamen**

*Mina Ryten*¹, Sebastian Gueiffi¹, Karishma D’Sa¹, Juan Botia³, Jana Vandrocova¹, Daniah Trabzuni¹, Adaikalavan Ramasamy², and The UK Brain Expression Consortium The UK Brain Expression Consortium ¹Colin Smith³, John Hardy¹, and Michael Weale⁴

**Background:** There is growing evidence to suggest that existing transcriptome references are incomplete for human brain. The aim of this study was to identify and characterise transcribed intergenic regions in two human brain tissues relevant to a range of neurological and neuropsychiatric disorders, namely putamen and substantia nigra.

**Methods:** We performed RNA-seq on post-mortem control human putamen (N=111) and substantia nigra samples (N=69). We used the Derfinder package to quantify transcribed regions in a reference-agnostic manner. After filtering, we combined the abundance of the intergenic transcribed regions with genotype information to perform cis-eQTL mapping. Using exon-junction identification and gene co-expression analysis, we investigated the independence of these regions from the nearest annotated genes and explored their function in silico.

**Results:** We detected 7.5Mb of intergenic expressed sequence within putamen (27K regions, 13.2% of annotated transcription) and 3.5Mb (16K regions, 7.1% of annotated transcription) within substantia nigra. We performed cis-eQTL analysis to detect 1954 independent cis-eQTL signals in putamen and 744 in substantia nigra, which target transcribed intergenic regions. We classified targeted regions as uncharacterised, independent or as probable novel exons/mis-annotations of known genes. We identified 41 genes implicated in rare Mendelian disorders amongst those with presumed novel/mis-annotated exons. Furthermore, we found a significant enrichment of GWAS risk SNPs amongst cis-eQTLs targeting transcribed intergenic regions as compared to known exons (p-value=3.2 x 10-7 in putamen).

**Conclusions:** Thus, we provide evidence for incomplete annotation of the transcriptome within adult human putamen and substantia nigra, as well as the disease relevance of the transcribed intergenic regions identified.

**Supported By:** Medical Research Council UK

**Keywords:** Basal Ganglia, RNA sequencing, expression quantitative trait loci (eQTL), gene co-expression network, Postmortem human brain

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**694. RNA-Seq Samples Beyond the Known Transcriptome with Derfinder Available via Recount**

*Leonardo Collado Torres*¹, Abhinav Nellore², Kai Kammers³, Shannon Ellis³, Margaret Taub³, Kasper Hansen³, Andrew Jaffe¹, Ben Langmead², and Jeff Leek³

¹Lieber Institute for Brain Development, ²Department of Computer Science, Johns Hopkins University, ³Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

**Background:** Differential expression analysis of RNA sequencing (RNA-seq) data typically relies on reconstructing transcripts or counting reads that overlap known gene structures. We previously introduced an intermediate statistical approach called differentially expressed region (DER) finder that seeks to identify contiguous regions of the genome showing differential expression signal at single base resolution without relying on existing annotation or potentially inaccurate transcript assembly. The first step is to align the RNA-seq reads to the genome which is costly and requires a solid computing infrastructure.

**Methods:** We implemented the DER finder approach in a R software package called derfinder which provides a computationally efficient bump-hunting approach to identify DERs that permits genome-scale analyses in a large number of samples. Using the Rail-RNA aligner we aligned over 70,000 human RNA-seq samples and summarized the results at the gene, exon, exon-exon junction and base pair-level coverage levels.

**Results:** We used derfinder to identify over 50,000 regions of the genome that are differentially expressed throughout the lifespan of the human brain with strong signal in non-exonic sections of the genome. We also developed the recount R software package that provides access to over 70,000 RNA-seq samples grouped in 2,041 projects.

**Conclusions:** The recount resource can be used for different levels of RNA-seq differential expression analysis without having the costly computational infrastructure for the alignment step. derfinder can be used with recount data or your own private data to perform annotation-agnostic RNA-seq analyses.

**Supported By:** R01 GM105705. LCT was supported by Consejo Nacional de Ciencia y Tecnologia Mexico 351535. Amazon Web Services experiments were supported by AWS in Education research grants. AEJ was supported by 1R21MH109956.

**Keywords:** RNA-seq, Genomics, Big data
DNA (DA) neurons in the ventral tegmental area (VTA) play a key role in controlling stress vulnerability. However, upstream mechanisms responsible for the functional control of these neurons remain unknown. Noradrenergic (NE) neurons from the locus coeruleus (LC), implicated in the pathophysiology of depression, have direct connections within the VTA. Here, we propose a thorough functional dissection of NE inputs from the LC converging to the VTA and address their role in driving vulnerability to chronic social defeat stress.

**Methods:** To this end, 10-day chronic social defeat stress was used in combination with i) circuit mapping tools, cfos immunohistochemistry and HPLC dosage, ii) engineered mice with selective brain-specific NE depletion (VMAT2DBHcre) mice and in vivo extracellular single-unit recordings of VTA-DA neurons and ii) optogenetic stimulation of LC-NE fibers in the VTA.

**Results:** We demonstrated a specific decreased activity of VTA-projecting LC-NE neurons in susceptible animals, associated with decreased VTA NE levels. Moreover, absence of NE signaling in VMAT2DBHcre renders these mice susceptible to the social defeat and induced an increase in neuronal excitability of VTA-DA neurons. These results demonstrated that the essential role of NE neurotransmission in promoting resilience likely occurred by inhibiting VTA-DA neuronal activity. Finally, optogenetic stimulation of LC-NE fibers in the VTA of susceptible mice triggers a switch toward resilience demonstrating that NE neurotransmission from the LC into the VTA is necessary and sufficient to promote resilience.

**Conclusions:** In conclusion, we characterized a new neural circuit underlying resilience to chronic stress and provided a potential new target for depression treatment.

**Supported By:** Canada Research Chairs programme, Graham Boeckh Foundation for Schizophrenia Research, Natural and Engineering Research Council of Canada (RGPIN 385732-2012), FRSQ

**Keywords:** Depression, Chronic Stress, Resilience, noradrenaline, Dopamine

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**SYMPOSIUM**

**Stress Vulnerability and Resilience: Integrating Neural Circuits, Molecular Mechanisms, and Clinical Signatures**

**Saturday, May 20, 2017 - 12:30 PM - 2:30 PM**

Sapphire IJ

Chair: Marco Andrea Riva
Co-Chair: Elisabeth Binder

**695. Resilience against Chronic Stress is Mediated by Noradrenergic Regulation of the Ventral Tegmental Area**

**Elsa Isingrini**1, Lea Perret1, Quentin Rainer1, Bénédicte Amilhon1, Elisa Guma1, Arnaud Tanti1, Garance Martin2, Jennifer Robinson1, Luc Moquin1, Fabio Marti2, Naguib Mechawar1, Sylvain Williams1, Alain Gratton1, and Bruno Girod2

1McGill University, Department of Psychiatry, 2McGill University, Department of Psychiatry/Sorbonne Universités, Paris

**Background:** Dopamine (DA) neurons in the ventral tegmental area (VTA) play a key role in controlling stress vulnerability. However, upstream mechanisms responsible for the functional control of these neurons remain unknown. Noradrenergic (NE) neurons from the locus coeruleus (LC), implicated in the pathophysiology of depression, have direct connections within the VTA. Here, we propose a thorough functional dissection of NE inputs from the LC converging to the VTA and address their role in driving vulnerability to chronic social defeat stress.

**Methods:** To this end, 10-day chronic social defeat stress was used in combination with i) circuit mapping tools, cfos immunohistochemistry and HPLC dosage, ii) engineered mice with selective brain-specific NE depletion (VMAT2DBHcre) mice and in vivo extracellular single-unit recordings of VTA-DA neurons and ii) optogenetic stimulation of LC-NE fibers in the VTA.

**Results:** We demonstrated a specific decreased activity of VTA-projecting LC-NE neurons in susceptible animals, associated with decreased VTA NE levels. Moreover, absence of NE signaling in VMAT2DBHcre renders these mice susceptible to the social defeat and induced an increase in neuronal excitability of VTA-DA neurons. These results demonstrated that the essential role of NE neurotransmission in promoting resilience likely occurred by inhibiting VTA-DA neuronal activity. Finally, optogenetic stimulation of LC-NE fibers in the VTA of susceptible mice triggers a switch toward resilience demonstrating that NE neurotransmission from the LC into the VTA is necessary and sufficient to promote resilience.

**Conclusions:** In conclusion, we characterized a new neural circuit underlying resilience to chronic stress and provided a potential new target for depression treatment.

**Supported By:** Canada Research Chairs programme, Graham Boeckh Foundation for Schizophrenia Research, Natural and Engineering Research Council of Canada (RGPIN 385732-2012), FRSQ

**Keywords:** Depression, Chronic Stress, Resilience, noradrenaline, Dopamine

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**696. Adult Hippocampal Neurogenesis Promotes Stress Resilience by Inhibiting Ventral Dentate Gyrus Activity**

**Christoph Anacker,** Victor Luna, Amira Millette, and Rene Hen

Columbia University & New York State Psychiatric Institute

**Background:** Adult hippocampal neurogenesis is necessary for antidepressant effects and for buffering stress responses. However, how the small population of adult-born neurons interacts with the majority of mature granule cells in the dentate gyrus to influence stress resilience is unknown.

**Methods:** We generated novel transgenic mouse lines to chemogenetically silence activity of either adult-born neurons or mature neurons in the dentate gyrus, using the inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADD), hM4Di. We examined anxiety-like behavior in the social interaction and open field tests, corticosterone levels, and dentate gyrus activity after 10 days of chronic social defeat stress.

**Results:** Social defeat increases anxiety-like behavior as measured by decreased social interaction (−40%, p = 0.008, n = 12) and decreased time in the center of the open field (−42%, p = 0.03, n = 12). Increasing neurogenesis counteracts stress-induced anxiety in these tests (p = 0.004, n = 13), while silencing adult-born neurons during stress enhances anxiety (p = 0.008, n = 9). After social defeat, corticosterone responses to subsequent acute stressors are blunted (−39%, p = 0.04, n = 12). These neuroendocrine abnormalities are counteracted by increasing neurogenesis (p = 0.04, n = 12), and exacerbated by silencing adult-born neurons (p = 0.03, n = 9). Social defeat increases the number of activated, c-fos+ mature granule cells specifically in the ventral dentate gyrus (p = 0.01, n = 8). This stress-induced elevated activity of mature neurons is reduced in mice with increased neurogenesis (p = 0.04, n = 8) and enhanced by silencing adult-born neurons (p = 0.02, n = 6). Such neurogenic inhibition of dentate gyrus activity is sufficient to promote stress resilience, as directly silencing mature granule cells reduces stress-induced anxiety (p = 0.04, n = 10) and neuroendocrine abnormalities (p = 0.03, n = 10).

**Conclusions:** Our findings demonstrate that hippocampal neurogenesis promotes stress resilience by inhibiting the ventral dentate gyrus.

**Supported By:** K99MH108719-01

**Keywords:** Neurogenesis, Chronic Stress, neural circuits, Resilience, Double transgenic mice

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**697. Testing the Three-Hit Hypothesis of Stress Susceptibility and Resilience in the Rat**

**Nikolaos Daskalakis**

Icahn School of Medicine at Mount Sinai

**Background:** Stressful experiences during perinatal and prepubertal life may increase psychosis vulnerability of individuals carrying genetic susceptibility for enhanced dopamine neurotransmission.
Methods: We tested this “three-hit” hypothesis of psychosis vulnerability in a rat line that was genetically selected for high apomorphine-susceptibility (APO-SUS) as the first-hit using Wistar rats as controls. Pups of both strains that received low maternal care, as judged from low maternal licking and grooming (LG) scores, respectively, were considered to suffer from the second-hit. As a third-hit the rats were exposed to post-weaning isolation-rearing, with social-rearing as the control condition. Psychosis readouts were apomorphine-induced gnawing and sensorimotor gating. All rats were also challenged with an acute subcutaneous injection producing stress levels of this glucocorticoid prior to sensorimotor gating measures. We finally assessed the prolactin stress-response and hippocampal gene-expression by RNA-sequencing.

Results: Adult APO-SUS rats displayed very high levels of apomorphine-induced gnawing. The APO-SUS Low-LG offspring that were reared in isolation displayed low acoustic startle and complete abolition of basal pre-pulse-inhibition (PPI), which was restored rapidly by CORT-treatment, and reduced prolactin response to stress. The APO-SUS High-LG offspring, on the contrary, displayed after isolation rearing the lowest apomorphine-induced gnawing counts, among the APO-SUS rats, and a normal acoustic startle and PPI, which were altered by the CORT-challenge. Hippocampal expression profiling suggested that the two groups differed in axonal guidance and GABA-receptor signaling.

Conclusions: Cumulative-stress exposure during development in individuals genetically-predisposed for enhanced dopamine responsiveness precipitates a psychosis-like phenotype, which is rapidly reversible by CORT, low prolactin stress-responsiveness and a compromised hippocampal function.

Supported By: Top-Institute Pharma T5 #209

Keywords: genetic predisposition, Early Life Stress, Social isolation, Sensorimotor Gating, Psychosis

698. Distinct miRNAs Signatures Associated with Stress Vulnerability and Stress Resilience in Childhood Trauma-Exposed Individuals

Annamaria Cattaneo, Nadia Cattane, Nicole Mariani, and Carmine Pariante
1Mind Research Network, University of New Mexico, 2Georgia State University, 3The Mind Research Network

Background: Stressful life events (SLEs), especially those occurring early in life, are well known risk factors for the development of stress-related disorders later in life. However, while susceptible individuals express inappropriate responses that may lead to psychopathology, resilient individuals develop adaptive responses for proper coping. The mechanisms underlying this difference are still poorly understood and may involve epigenetic processes, including miRNAs.

Methods: In this study we have analysed, by using Affymetrix platform and arrays, the entire miRNOME in blood samples of 40 subjects exposed to childhood trauma and characterized for stress coping abilities. Moreover, the miRNAs that have been found associated with stress-related vulnerability have been analysed also in blood samples of patients with depression (n=20) and in patients with borderline personality disorder (n=20).

Results: Data have been analysed by using Partek Genomic Suite and identified distinct miRNAs signatures associated with vulnerability or resilience to stress. Importantly, a panel of 15 miRNAs, including the miR-15a and miR-34c, that we found associated with stress vulnerability, have been found altered also in blood samples of patients with depression and with borderline personality disorder.

Conclusions: Our data suggest that miRNAs can mediate the long term effects of SLEs exposures and that the modulation of specific miRNAs can underlie resilience or vulnerability to stress. MiR-15a and miR-34c, that have been found modulated in stress-vulnerable subjects are altered also in patients with stress-related disorders, suggesting that targeting specific miRNAs may have preventive effects in vulnerable subjects.

Supported By: Eranet-neuron 2013 to AC; Ministry of Health to AC.

Keywords: Childhood Trauma, miRNAs, stress related disorders
scale gray matter networks and to dynamic functional network connectivity.

**Conclusions:** Our results are consistent with the idea that just as schizophrenia is a polygenic disorder, the imaging differences that contribute to it are also polygenic. Multivariate approaches provide a powerful way to study such links. The ability to examine the combined effects of multiple small genetic effects allows us to assess genetic pathways for potential mechanisms of multiple patterns of brain imaging effects in schizophrenia.

**Supported By:** This work was in part funded by NIH via a COBRE grant P20GM103472, R01 grants REB020407 and R01MH094524, and NSF grant 1539067.

**Keywords:** Schizophrenia, Genetics, Brain Imaging, Epigenetics, multivariate analysis

700. Genetic Overlaps between Schizophrenia and Cognition in Asia

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**Background:** Cognition and neuropsychiatric diseases are highly polygenic and pleiotropic. Examining genetic overlaps between schizophrenia and cognitive phenotypes could further the biological and functional role of schizophrenia associated markers.

**Methods:** A sample of 3547 subjects (n = 1672 cases) was analyzed. Genetic overlaps were examined using Transethnic Genetic Correlation (Brielin et al., 2016). Leave-one-out PGC2 schizophrenia summary statistics were utilized for meta-analysis with cognitive phenotypes in subjects with cognitive data. QC and imputation analysis were carried out via Ricopili. Meta-analysis was performed in METAL.

**Results:** Transethnic Genetic Correlation revealed significant genetic correlations between the PGC and Singapore schizophrenia data (rge = .56; p = 9.47e-4). 52 markers that are part of the PGC 128 schizophrenia-associated loci, or in LD with the loci were enriched by cross-phenotype meta-analysis. Preliminary pathway analysis of the overlapping PGC and cognition markers revealed significant pathways associated with i) nicotinic/acyethylcholine (p = 1.75e-5) (ii) calcium channel/ion channel (p = 2.51e-3) iii) DNA methylation (p = 4.07e-3) iv) chromatin modification (p = 5.25e-3). Gene set analysis using data from the Allen Human Brain Atlas revealed 7 candidate regions spanning the occipital-temporal regions (AUC = .67; p = 0.042).

**Conclusions:** Results from the current analysis support evidence that has previously been reported in both schizophrenia and cognitive literature. The results provide potential biological insights to the understanding of cognitive impairments found in schizophrenia. Further research is necessary to replicate the current findings at both clinical and biological levels and refine analytical methods reported here.

**Supported By:** NMRC Grants: NMRC/TCR/003/2008; MH095: 003/008-1014; NMRC/CG/004/2013

**Keywords:** Schizophrenia, Cognition, Pleiotropy, GWAS, LD regression

701. Schizophrenia Genetic Risk Factors Are Associated with Cognitive Functions in the GENUS Consortium Collection

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**Background:** Recent large-scale genetic studies have identified compelling genetic risk factors for schizophrenia, however their function in disease is largely unknown. The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium is examining the role of these risk variants in cognitive functions relevant to the disorder.

**Methods:** Sixteen international research groups contributed genotype, clinical, and neuropsychological data from 4,167 schizophrenia patients, 324 familial high-risk individuals, and 2,677 healthy controls. Genome-wide SNP data underwent quality control and 1000Genomes imputation. Neuro-psychological test data were harmonized across samples by pooling controls, regression model fitting, residualization and standardization relative to controls. Eight cognitive domain composite scores were computed using all tests categorized within each domain. General cognitive ability, ‘g’, was generated using all available tests within each site (first principal component). Individual SNPs, polygenic pathways, and polygenic risk scores were tested for association with each cognitive phenotype using linear regression.

**Results:** Schizophrenia patients performed significantly worse than controls on all 8 cognitive domains and ‘g’ (p<.001). Analyses of 108 schizophrenia risk SNPs identified associations with several cognitive domains and ‘g’ (FWE-corrected p<5E-5). Nominal associations were detected for synapse and immune/neuronal signaling pathways implicated in schizophrenia (uncorrected p<.05). Polygenic risk for schizophrenia explained significant variance in ‘g’ and 7 cognitive domains (R² = 0.6-2.1%; p = 0.033-1E-6).

**Conclusions:** Significant association of schizophrenia genetic risk factors with cognitive phenotypes provides initial insight into the role of schizophrenia risk genes in brain function underlying psychopathology. Genetic overlap between schizophrenia and cognition suggests that shared genes may regulate neural processes mediating both cognition and psychosis.

**Supported By:** R01MH092380

**Keywords:** Schizophrenia, Genetic Association, Cognitive Impairment, Polygenic Risk, single-nucleotide variation

702. The Behavioural and Neural Correlates of Social Cognition in Youth with Mental Illness

Laura Stefanik¹, Stephanie Amenis¹, Benoit Mulsant¹, Anil Malhotra², Robert Buchanan³, Tarek Rajji¹, George Foussias¹, and Aristotle Voinoskos¹

¹Centre for Addiction and Mental Health, University of Toronto, ²The Zucker Hillside Hospital, ³Maryland Psychiatric Research Center
Background: Schizophrenia (SSD), autism spectrum disorders (ASD), and bipolar disorder (BD) share vulnerability and genetic underpinnings yet there is considerable heterogeneity in social cognitive performance and social function within and across these disorders. This work aims to identify subgroups of patients across disease-based groups that share similar impairments in social cognition and brain structure in order to identify therapeutic targets.

Methods: A sample of 32 adolescents and young adults with SSD, 20 with verbal ASD without intellectual disability, 17 with euthymic BD, and 41 controls completed social and non-social cognitive tasks. Structural and diffusion weighted images were acquired and these data were integrated using Similarity Network Fusion (Wang et al., 2014).

Results: The fused network revealed five subgroups with significant differences in social cognitive performance and fractional anisotropy (FA) of white matter tracts central to social-emotional processing such as the uncinate fasciculus (p<0.001) and genu of the corpus callosum (p=0.005). A young male-dominant group, largely comprised of youth with ASD and SSD, had the lowest FA in the uncinate and most impaired social cognitive performance; particularly for the most complex test (Welch’s F(4,38)=10.91, p<0.001). An ASD-dominant mixed-sex cluster had average to high performance on the social cognitive and memory subtests but the worst performance for the processing speed domain (Welch’s F(4,44)=7.399, p=0.001).

Conclusions: Using transdiagnostic and data integration approaches we can successfully identify biologically informed subtypes which may reflect distinct genetic mechanisms that cross diagnostic boundaries. These findings may help drive new hypotheses for studies interested in identifying therapeutic targets for social cognitive deficits.

Supported By: R01MH102324
Keywords: Social Cognition, Structural MRI, Youth, Imaging genetics, Similarity Network Fusion

704. Circadian Clock Genes and Lithium Response in Bipolar Disorder

Michael McCarthy
University of California San Diego

Background: Circadian rhythm abnormalities are a central clinical feature of bipolar disorder (BD), affecting rhythms in sleep and activity. The mood stabilizer lithium corrects circadian rhythm abnormalities in bipolar disorder and changes the expression of “clock genes” that direct rhythms. However, the role of clock genes in bipolar disorder is unknown, and it is unclear if lithium’s effects on rhythms are relevant to treatment outcomes.

Methods: 60 subjects with BD completed a 2 yr maintenance trial of lithium monotherapy and donated fibroblast cell lines. Using a bioluminescent circadian reporter gene, circadian rhythms were measured in patient and healthy control fibroblasts at high sampling density over 5 days, under lithium treated and untreated conditions. Differences in cellular rhythms were examined in the context of the donor’s lithium treatment outcome and genetics.

Results: Rhythm amplitude under lithium treated conditions discriminated BD patients and controls. Among BD patients, rhythm period length discriminates lithium responders from non-responders. Genetic factors predicted some of the individual differences in circadian rhythms.

Conclusions: Circadian rhythm abnormalities are detectable in cells from BD patients. Individual differences in circadian rhythms may influence the efficacy of lithium in preventing mood relapse during maintenance therapy.

Supported By: Dept Veterans Affairs/ORD Career Development Award
Keywords: Lithium, Bipolar Disorder, Circadian Rhythms

705. Using iPS Derived Neurons and GWAS Together to Identify Genes for Lithium Response

John Kelsoe1, Mike McCarthy1, Caroline Nievergelt1, Paul Shilling2, John Nurnberger3, Elliot Gershon4

Background: Lithium response varies greatly among bipolar individuals. There has been very few findings to explain this variation. Genetic and biological factors have been suggested to be important. Stressful events are known to shorten telomeres in many tissues including brain cells. Lithium has been suggested to be a neuroprotective agent.

Methods: Telomere and telomerase analysis combined with genetic, biochemical and expression analysis has been used to study both humans with bipolar disorder, controls and animal tissue.

Results: We have identified a novel pathway involving telomere variation and telomere length that predict Li response in a longitudinal study as well as genetic variants associated with telomere length in bipolar disorder. The results have been replicated in a Brazilian cohort. In total over 1000 subjects were studied. A marked reduction in shortening of telomere size was observed (p 0.001).

Conclusions: Telomere dynamics relate to Lithium response and is a biomarker improving precision in medical treatment of bipolar disorder. The pathway activated by lithium involves beta-catenin, BDNF and telomerase activation. The effect may be neuroprotective.

Supported By: Swedish Research Council
Keywords: telomerase, beta-catenin, bipolar disorder, telomere size
Background: The Pharmacogenomics of Bipolar Disorder study was started with the notion that biological information from iPS derived neurons could be used in combination with GWAS in order to efficiently identify genes associated with lithium response.

Methods: 585 patients with Bipolar I were treated with lithium at 11 sites with the goal of stabilization on monotherapy in 4 months. Those who were stabilized were then followed for two years in order to detect relapse. DNA was obtained and genotyped using the PsychArray for GWAS, while three clear responders, three clear non-responders and four control subjects were signifi
cantly associated to response in this analysis.

Results: All neurons from bipolar subjects demonstrated a threefold increase in spontaneous action potentials which was rescued by lithium in cells from responders but not non-responders. RNAseq was conducted on the cells and 462 genes identified whose expression was signifi
cantly altered by lithium, and CBARP was significantly associated to response in this analysis.

Conclusions: CBARP modulates the voltage gated calcium complex and is consistent with existing GWAS results. By using a priori information from iPS gene expression, the number of tests was greatly reduced and power increased. These results argue for such combined strategies where appropriate models exist.

Supported By: NIMH; NARSAD

Keywords: WNT signaling, Lithium associated molecular changes, GSK-3β, Affective Disorders, Mouse model

706. Wnt/β-Catenin Pathway Contributions to Dendritic Spine and Glutamatergic Synapse Formation Responsive to Lithium-Mediated GSK3 Inhibition

Robert Stanley1, Pierre-Marie Martin1, Adam Ross1, Andiara Freitas1, Jillian Iafrati1, Caitlin Moyer2, Audrey Brumbach1, Mehdi Pirooznia3, W. Richard McCombie4, James Potash3, Peter Zandi3, Shaun Purcell6, Stephan Sanders1, Yi Zuo6, Vikaas Sohal1, and Benjamin Cheyette1

1UCSF, 2UCSC, 3Johns Hopkins University, 4Stanley Institute (Cold Spring Harbor Laboratory), 5University of Iowa, 6Harvard

Background: A major direct target of lithium is the metallocenzyme GSK3, the central kinase in the Wnt/β-catenin pathway broadly involved in neural development.

Methods: We have investigated neurodevelopmental and behavioral functions of DIXDC1, which regulates Wnt/β-catenin signaling including late in neural development and postnatally. We have studied a Dixoδ1 knock-out (KO) mouse line, applying in vitro and in vivo experimental approaches to assess neurodevelopment, neural activity, dendritic spine dynamics, animal behavior, and responsiveness to lithium and a selective GSK3 inhibitor. This has been accompanied by sequencing of the human DIXDC1 locus in several psychiatric disorders including bipolar disorder, and rescue and gain-of-function experiments involving rare human missense single nucleotide variants (SNVs) that alter the protein’s signaling activity.

Results: In mice, loss of Dixoδ1 leads to dose-sensitive deficits in behavioral assays including models of depression; this is responsive to lithium as well as to a selective GSK3-inhibitor. Forebrain cortical pyramidal neurons from Dixoδ1KO mice have reduced dendritic spine and glutamatergic synapse density correctable by lithium or a selective GSK3 inhibitor. Many of the rare SNVs found more frequently in psychiatric patients affect Wnt/β-catenin activity of the encoded protein. They also alter the above neurodevelopmental parameters when expressed in differentiating pyramidal neurons.

Conclusions: Our data support a role for DIXDC1 in formation and/or stability of dendritic spines and synapses in forebrain pyramidal neurons upstream of complex behaviors including depression. Our data further suggest that this occurs through the protein’s activity in the Wnt/β-catenin signaling pathway within neurons, and that this responds to GSK3 inhibition by lithium.

Supported By: R01, R01 supplement, K01, T32, Simons Foundation (SFARI), BBRF (NARSAD), Brazilian National Council for Scientific and Technological Development

Keywords: WNT signaling, Lithium associated molecular changes, GSK-3β, Affective Disorders, Mouse model
Methods: We performed GWAS of PTSD using the Clinician Administered PTSD Scale in the Systems Biology Biomarker cohort and conducted replication and follow-up studies in an external sample, a larger urban community cohort, to determine the robustness and putative functionality of this risk variant, associated with differential epigenetic regulation and differential cortical responses to fear.

Results: In this study with an extreme phenotype design, we found a genome-wide significant SNP to associate with the Clinician Administered PTSD Scale. We will also review other recent findings on the role of noncoding RNAs in regulating protein-coding genes involved in stress regulation. Finally, we will review recent progress in genetic pathway analyses and gene x environment interactions as additional approaches to identify mechanisms of heritability for stress-related disorders.

Conclusions: Together, these findings provide new insight into understanding genetic and epigenetic regulation of PTSD and its intermediate phenotypes.

Supported By: DOD

Keywords: Genetic Association, PTSD - Posttraumatic Stress Disorder, Biomarkers, Epigenetics, long non-coding RNA

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709. Increased Circulating Blood Cell Counts in Combat-Related PTSD: Associations with Inflammation and Symptom Severity

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1Lund University/UCSF, 2UCSF, 3University of Miami, 4James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, 5UCSF/Veterans Affairs Medical Center, San Francisco, 6NYU, 7Sapienza University

Background: Cytokine levels are increased in post-traumatic stress disorder (PTSD), but their relationship to circulating blood cell counts is unknown.

Methods: 163 male combat-exposed veterans (83 with PTSD and 81 non-PTSD controls) had blood assessed for platelet count, white blood cell (WBC) count, and red blood cell (RBC) count. These data were correlated with symptom severity and with pro-inflammatory markers.

Results: Platelet count (p = 0.028), WBC (p = 0.004) and RBC (p = 0.003) were significantly elevated in PTSD. Pro-inflammatory blood markers were significantly correlated with WBC count in both groups (PTSD, r = 0.26, p = 0.022; controls, r = 0.46; p < 0.001), platelet count in PTSD subjects only (r = 0.32, p = 0.004), and RBC count in PTSD subjects and controls combined (r = 0.21; p = 0.009). PTSD symptom severity ratings were directly correlated with platelet count in the PTSD group (r = 0.30, p = 0.007). When smoking was entered as a covariate, the between-group differences in cell counts became non-significant, although all correlations between cell counts and PTSD severity and inflammatory markers remained significant, with the exception of the correlation between RBC and inflammatory markers.

Conclusions: Patients with PTSD have elevated counts of platelets, WBC and RBC. This is at least partly mediated by smoking status. The association of platelet count with inflammation in PTSD, but not in controls, may relate to the...
increased pro-thrombotic risk, associated with inflammation, in PTSD. The potential importance of increased platelet counts in PTSD is bolstered by its significant positive correlation with PTSD symptoms severity.

**Supported By:** This study was supported by the following grants: U. S. Department of Defense, W81XWH-11-2-0223 (PI: Charles Marmar); U. S. Department of Defense, W81XWH-10-1-0021 (PI: Owen M. Wolkowitz); The Mental Illness Research, Education and Clinical Center (MIRECC). Daniel Lindqvist was supported by the Swedish Research Council (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:** PTSD, Platelet, white blood cells, Inflammation, combat

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**710. Neuroendocrine and Molecular Markers and PTSD**

Rachel Yehuda\(^2\) and Janine Flory\(^1\)

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**Background:** Enhanced glucocorticoid receptor (GR) sensitivity is present in people with PTSD but the molecular mechanisms of GR sensitivity are not understood. Epigenetic factors have emerged as one potential mechanism that account for how trauma exposure leads to PTSD.

**Methods:** We compared neuroendocrine and epigenetics markers in male and female OEF/OIF veterans with PTSD (PTSD+) and matched combat-exposed controls without PTSD (PTSD-).

**Results:** The PTSD+ group showed greater evidence of glucocorticoid receptor (GR) sensitivity in PBMCs as reflected by the lysozyme stimulation test, compared to the PTSD- group. Evidence of greater GR sensitivity was also reflected in the results of the dexamethasone suppression test (DST) as the veterans with PTSD showed a greater decline in cortisol in response to 0.50 mg DEX. Results of 24-hr urinary cortisol excretion showed that the PTSD+ veterans tended to have lower urinary cortisol excretion. Additionally, we examined cytosine methylation of the 1F promoter of the GR gene, a molecular epigenetic marker. Results showed that a significantly lower percentage of methylated clones was observed in the NR3C1-1F promoter across the 39 CpG sites in the PTSD+ compared to the PTSD- group. Percent methylated clones and sum percent methylation were inversely correlated with cortisol decline in response to DEX.

**Conclusions:** There were few sex differences, as male and female combat veterans with PTSD showed similar patterns for measures of GR sensitivity and methylation. In conclusion, there is a neuroendocrine signature associated with combat-PTSD that is fairly reliable in discriminating groups of persons with and without PTSD.

**Supported By:** DOD

**Keywords:** PTSD, Biomarkers, Epigenetics, Glucocorticoid receptor, Neuroendocrine

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**SYMPOSIUM**

**Mapping (and Modulating) Memory Circuitry in Depression, Anxiety, and Psychosis**

**Saturday, May 20, 2017 - 12:30 PM - 2:30 PM**

**Aqua 300 AB**

**Chair:** Daniel Dillon

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**711. The Impact of Depression on Brain Activity during Source Memory Retrieval**

Daniel Dillon and Elyssa Barrick

McLean Hospital/Harvard Medical School

**Background:** Recollection is disrupted in Major Depressive Disorder (MDD), but this disruption can be minimized by focused attention at encoding and retrieval. The neural mechanisms responsible for these clinically important phenomena are unclear. Thus, we used event-related potentials (ERPs) to examine recollection in MDD.

**Methods:** Twenty-four unmedicated adults with MDD and 24 controls encoded words shown on the left or right (perceptual source) by making animacy or mobility judgments (conceptual source). ERPs were recorded during cued source retrieval, which depends on recollection.

**Results:** Mobility judgments prompted deeper encoding than animacy judgments, and memory accuracy was characterized by a Group x Cue x Encoding Task interaction: depressed adults were generally less accurate and less confident than controls, but they showed excellent conceptual source memory following deeper encoding. In parallel, a positive parietal ERP deflection that tracks recollection was globally reduced in depression, but sustained left parietal activation was seen during conceptual source judgments for deeply encoded words in MDD.

**Conclusions:** This study links two reliable effects of depression on recollection to electrophysiological activity over parietal cortex. First, accuracy and confidence were reduced in MDD, and the most reliable ERP correlate of recollection—a positive parietal deflection from 400-800 ms—was blunted. Second, depressed adults showed excellent memory when the encoding and retrieval tasks demanded sustained attention, and this combination elicited lasting left parietal activity. These results link the impact of depression on recollection to parietal circuits that communicate with the hippocampus, highlighting the need for further work on this important topic.

**Supported By:** R00 MH094438-03; internal funding from McLean Hospital

**Keywords:** Depression, Memory, Retrieval, ERP, Recollection

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**712. Emotional Modulation of the Neural Systems Supporting Episodic Memory**

Maureen Ritchey\(^1\), Andrew Yonelinas\(^2\), and Charan Ranganath\(^2\)

\(^1\)Boston College, \(^2\)UC Davis
713. Aberrant Mesolimbic-Hippocampal Interactions in First-Episode Psychosis

Vishnu Murty, Maria Jalbrzikowski, David Montez, and Beatriz Luna

University of Pittsburgh

**Background:** Psychosis is associated with complex patterns of changes in dopamine-mediated behaviors, including aberrant salience detection and decreased reward motivation, in addition to deficits in episodic memory. Prominent animal models suggested that these deficits may emerge from dysfunctional regulation of ventral tegmental area (VTA), which has downstream consequences on the hippocampus. Relatively little research, however, has investigated this pathway in humans. In the talk, I will present work characterizing network connectivity between mesolimbic and hippocampal systems in first-episode psychosis.

**Methods:** Resting-state, multi-band fMRI data was collected in 56 volunteers (1st-episode psychosis: 29, matched controls: 27). Functional connectivity of the VTA with hippocampus, prefrontal cortex, and nucleus accumbens was characterized. Connectivity deficits were associated with positive symptoms, negative symptoms, and episodic memory.

**Results:** Individuals with first-episode psychosis showed greater connectivity between the VTA and hippocampus (p<0.05), as well as a pronounced influence of VTA over the hippocampus for extended periods of time (p<0.05). Deficits in VTA-hippocampal connectivity also predicted negative symptoms (P<0.005) and executive function deficits (p<0.05) in the psychosis population.

**Conclusions:** Our findings characterize deficits in mesolimbic-hippocampal network connectivity in 1st-episode psychosis. The findings promote a model of increased neuromodulation of the VTA over the hippocampus in psychosis, which results in aberrant information processing across this circuit. Critically, this circuit dysfunction could contribute to known clinical and cognitive symptomatology present in psychosis.

**Supported By:** P50 NIMH103204

**Keywords:** Hippocampus, Episodic Memory, Ventral Tegmental Area, First Episode Psychosis, Resting state fMRI

714. Modulating Positive and Negative Memories to Suppress Psychiatric Disease-Like States

Steve Ramirez1 and Briana Chen2

1Harvard University, 2Columbia

**Background:** Chronic stress affects numerous brain areas involved in memory, emotion, and motivation, such as the hippocampus, amygdala, and prefrontal cortex; it abnormally alters a variety of cellular events, including dendritic morphology and gene expression patterns; and, it can precipitate several maladaptive states, such as depression- and anxiety-like behaviors. Yet, the neural circuitry sufficient to mitigate or even prevent such phenotypes is unclear. In both mice and humans, the hippocampus has been implicated in storing and retrieving positive memories and in modulating stress-related states.

**Methods:** We utilized a virus system in which the promoter of the immediate early gene c-Fos drives the expression of the light-sensitive ion channel channelrhodopsin-2 in a manner that is under the control of the antibiotic Doxycycline. In the absence of Doxycycline, learning-induced neuronal activity selectively labels active c-Fos-expressing neurons with channelrhodopsin-2, thus conferring activity-dependent and inducible labeling of, in addition to optical control over, hippocampus cells and their corresponding axon terminals.

**Results:** Optically modulating a defined set of positive or negative memory bearing hippocampus cells was sufficient to ameliorate or mimic the effects of chronic stress at the cellular and behavioral levels. Moreover, chronically activating negative memories in the dorsal or ventral hippocampus was sufficient to extinguish or enhance the associated behavioral expression of fear, respectively, and in a context-specific manner (N = 8 per group; student’s t-test).

**Conclusions:** We propose that optically activating positive or negative memories offers a potential therapeutic node for mitigating the effects of chronic stress on circuits and behavior.
715. Neurons from Bipolar Disorder Patients Are Characterized by Intrinsically Different Sub Populations of Neurons

Fred Gage, Shani Stern, Renata Santos, Maria Carol Marchetto, Ana Diniz Mendes, Guy Rouleau, Steven Biesmans, Qiwen Wang, Jun Yao, Patrick Charnay, Anne Bang, and Martin Alda

1The Salk Institute, Lab of Genetics, 2Montreal Neurological Institute, Department of Neurology and Neurosurgery, McGill University, 3Conrad Prebys Center for Chemical Genomics, Sanford Burnham Prebys Medical Discovery Institute, 4State Key Laboratory of Membrane Biology, Tsinghua-Peking Joint Center for Life Sciences, School of Life Sciences, IDG/McGovern Institute for Brain Research, Tsinghua University, 5Ecole Normale Supérieure, PSL Research University, CNRS, Inserm, Institut de Biologie de l’Ecole Normale Supérieure (IBENS), 6Department of Psychiatry, Dalhousie University

Background: Bipolar disorder (BD) is a progressive psychiatric disorder with more than 3% prevalence worldwide. Affected individuals experience recurrent episodes of depression and mania, disrupting normal life and increasing the risk of suicide greatly. The complexity and genetic heterogeneity of psychiatric disorders have challenged the development of animal and cellular models. We recently reported that hippocampal dentate gyrus (DG) neurons differentiated from induced pluripotent stem cell (iPSC)-derived fibroblasts of BD patients are electrophysiologically hyperexcitable.

Methods: Here we used iPSCs derived from Epstein-Barr virus (EBV)-immortalized B-lymphocytes to verify that the hyperexcitability of DG-like neurons is reproduced in this different cohort of patients and cells. Additionally, we used whole cell patch clamp recordings of over 460 neurons to characterize neurons derived from control individuals and BD patients.

Results: Extensive functional analysis showed that intrinsic cell parameters are very different between two groups of BD neurons, those derived from Lithium responsive (LR) patients, and those derived from Lithium non-responsive (NR) patients, partitioning this disorder into two sub populations of cells. Despite the very different functional profile, both populations of neurons share a large fast After-hyperpolarization (AHP).

Conclusions: We therefore suggest the large fast AHP as a key feature in BD, and a main contributor to the fast, sustained spiking abilities of BD neurons. Confirming our previous report with fibroblast-derived DG neurons, chronic Lithium treatment reduced the hyperexcitability in the lymphoblast-derived LR group but not in the NR group, strengthening the validity and utility of this new human cellular model of BD.

Supported By: NIH Early Independence Award; NARSAD; Ludwig Family Foundation
Keywords: Memory, optogenetics, Hippocampus, psychiatric disorders, Stress

716. Abnormal Calcium Signaling Dynamics in iPSC-Derived Bipolar Disorder Neurons

Aislinn Williams, Austin Smarsh, Victor Cazares, Katarzyna Glanowska, Cynthia Delong, Monica Barne, Emily Martinez, Kim-Chew Lim, Rachel Parent, Edward Stuenkel, Melvin McInnis, Geoffrey Murphy, and K Sue O’Shea

University of Michigan

Background: A major challenge in understanding neuropsychiatric disorders has been the lack of viable cells and tissues to analyze. Patient-derived induced pluripotent stem cells (iPSC) offer the opportunity to examine neural tissues and the prospect of identifying underlying disease mechanisms. We previously reported alterations in ion channel mRNA levels in BD neurons, specifically increased mRNA for the calcium channel gene CACNA1C.

Methods: To study bipolar disorder (BD), we have derived and characterized iPSC from fibroblasts from controls (C) and BD patients, and differentiated them into neurons and astrocytes. We use fluorescent calcium indicators to measure differences in spontaneous and evoked calcium signals in BD versus C neurons. We are using these cell models to investigate the role of a SNP in CACNA1C, a risk factor for BD, in neuronal function by using CRISPR/Cas9 to generate isogenic iPSC lines.

Results: BD neurons have greater calcium transients in response to potassium-induced depolarization compared to C neurons, and lithium pre-treatment reduces these calcium transients to levels observed in C neurons. Current investigations are in progress to examine activity evoked by field stimulation in cortical neurons. One potential BD therapeutic, ketamine, may alter calcium signals in neurons, and we are using our cell models to assess how ketamine affects patterning and differentiation in BD and C neurons.

Conclusions: Our iPSC model demonstrates that BD cortical neurons display abnormal calcium signaling dynamics compared to C neurons. Different modes of stimulation may influence assay readout, underlining the importance of technique standardization, a major goal of our NIMH-funded consortium.

Supported By: MH106434, KL2TR000434, UL1TR000433, Prechter Bipolar Research Fund
Keywords: Bipolar Disorder, iPSC, Calcium, CACNA1C

717. Using Human iPSCs for Psychiatric Disorder Disease Modeling and Mechanism-Based Drug Discovery

Zhexing Wen, Ziyuan Guo, Xinyuan Wang, Namshik Kim, Christopher Ross, Russell Margolis

Supported By: NIMH Early Independence Award; NARSAD; Ludwig Family Foundation
Keywords: Memory, optogenetics, Hippocampus, psychiatric disorders, Stress

SYMPOSIUM
iPSC-Based Platform Development for Major Psychiatric Disorder Modeling and Discovery

Saturday, May 20, 2017 - 12:30 PM - 2:30 PM
Aqua AB
Chair: Hongjun Song
Co-Chair: Guang Chen
Kimberly Christian1, Gong Chen3, Wei Zheng4, Menghang Xia4, Hongjun Song1, and Guo-li Ming1

1Johns Hopkins University, 2Johns Hopkins University, Emory University, 3The Pennsylvania State University, 4National Center for Advancing Translational Sciences

**Background:** To investigate genetically-mediated risk for psychiatric disorders and its biological substrates, we focused on a rare, penetrant mutation in DISC1, a gene associated with increased susceptibility for schizophrenia and affective disorders. We first generated induced pluripotent stem cell (iPSC) lines from members of an American family with and without a 4 basepair (bp) deletion in DISC1, as well as isogenic lines in which the mutation had been corrected or introduced. Upon differentiation to mature glutamatergic cortical neurons, we identified a causal role of DISC1 in mediating synaptic development and transcriptional regulation of many genes associated with synaptic function and psychiatric disorders.

**Methods:** Our initial RNA-sequencing results revealed upregulation of several phosphodiesterases (PDEs) in neurons with the DISC1 mutation. Because PDEs regulate synaptic development and function, we screened for PDE inhibitors that could ameliorate the phenotypes we observed in the mutant neurons.

**Results:** Rolipram, a PDE4 inhibitor, largely reversed synaptic deficits observed in mutant neurons including presynaptic protein expression, structural formation of synapses, activity-dependent vesicle release and spontaneous and evoked electrophysiological activity. The same drug treatment had little to no effect on neurons without the mutation.

**Conclusions:** Our study shows how patient-specific iPSCs can be used for biological discovery and identification of new drug candidates based on hypothesis-driven investigations. We are working with our partners to determine whether these results generalize across different patient cohorts and to develop scalable assays for an eventual iPSC-based drug evaluation platform.

**Supported By:** NIMH (U19 MH106434); MSCRF

**Keywords:** Schizophrenia, hPSC, synapses, disease modeling

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**719. Deep Brain Stimulation for Treatment Resistant Depression – Where Are We Coming From?**

**Thomas Schlaepfer**1, Volker Coenen2, and Bettina Bewernick3

1University Hospital, 2University of Freiburg, 3University Hospital Bonn, Germany

**Background:** Small studies and case series on deep brain stimulation (DBS) in treat-ment-resistant depression have reported positive results. However, two pivotal studies have been halted early on because of failed futility analyses.

**Results:** Results from two studies stimulating at the superolateral medial forebrain bundle (slMFB) will be presented. These critically reviewed data will be used as basis for a
presentation of the study design of the actually planned larger randomized-control trial (RCT) stimulating at the siMFB.

**Methods:** 16 TRD patients were stimulated with DBS to the siMFB. Patients were stimulated immediately (group A) or after two months (group B). Primary outcome criterion was the difference in antidepressant response between groups during sham phase and during long-term effect of open 12 months DBS.

**Results:** A significant difference in antidepressant effect compared to baseline was found in the first month for both groups. In the second month, only group A showed a significant antidepressant response. A significant antidepressant effect for each month of DBS compared to baseline was found after DBS onset. Main side effect was strabismus at higher stimulation currents.

**Conclusions:** This first RCT stimulating the siMFB confirmed previous efficacy data from our group in a smaller sample of eight patients and data from colleagues on four patients. For three weeks, some of the sham-stimulated patients showed a significant response. These findings are discussed and our new adapted trial design (including staggered onset, withdrawal of stimulation after parameter optimization) for the next multicenter RCT will be presented here.

**Keywords:** Treatment Resistant Depression, medial forebrain bundle, deep brain stimulation, randomized control study design

720. Open Label and Controlled Trials of Deep Brain Stimulation (DBS) at the Ventral Capsule/Ventral Striatum (VC/VS) for Treatment Resistant Depression (TRD)-Data and Technical Issues in Trial Planning

Darin Dougherty

Harvard Medical School

**Background:** Dr. Dougherty will discuss both open label and controlled trials of deep brain stimulation (DBS) at the ventral capsule/ventral striatum (VC/VS) for treatment resistant depression (TRD). While open label results were encouraging, the controlled trials at this site were negative.

**Methods:** After presenting these results, Dr. Dougherty will discuss possible reasons for the controlled trial failure as well as alternative approaches for future trials. Possible reasons for negative results include the possibility that the intervention is not an efficacious treatment for TRD, issues with patient selection in a highly heterogenous population, and trial design issues.

**Results:** Possible reasons for negative results include the possibility that the intervention is not an efficacious treatment for TRD, issues with patient selection in a highly heterogenous population, and trial design issues.

**Conclusions:** Dr. Dougherty will discuss potential alternative trial designs, especially in light of published positive controlled trial results at this target in a blinded withdrawal trial design. Lastly, Dr. Dougherty will discuss alternate DBS for TRD approaches from a broader perspective, including alternate targets (e.g., MFB) and closed loop DBS control strategies.

**Keywords:** Deep Brain Stimulation, VC/VS, treatment resistant depression, trial design, closed loop stimulation

721. Target Selection in Deep Brain Stimulation: Prospective Use of Tractography Simplifies a Critical Variable of Efficacy

Patricio Riva Posse1, Kisueng Ch2, Andrea Crowell2, Robert Gross2, and Helen Mayberg3

1Emory University Department of Psychiatry, 2Emory University, 3Emory University School of Medicine

**Background:** Randomized controlled trials (RCTs) of deep brain stimulation (DBS) in treatment-resistant depression (TRD) have failed to deliver the promising results described in open-label case series. Trial design in DBS faces more challenges than pharmacological RCTs. Target identification and contact selection are known contributors to variability in efficacy across different indications for DBS surgery. Responders to DBS in the subcallosal cingulate (SCC) share stimulation on a stereotypic connectome of converging white matter bundles (forceps minor, uncinate fasciculus, cingulum and frontostratial fibers). Implementation of tractography-based target selection using a “connectome blueprint” of past responders to DBS may improve outcome and simplify parameter selection.

**Methods:** Preoperative MRI, including DTI, was acquired in 17 patients with TRD who received SCC DBS. Before surgical implantation, the necessary white matter tracts were identified in each patient. Deterministic tractography was used to visualize fiber tracts in the SCC. A postsurgical CT was used to confirm location of the electrodes, and a tractographic common map was made to verify the similarity with the retrospective blueprint.

**Results:** The common probabilistic tract map generated for responders demonstrated inclusion of the four tracts, matching the “responder connectome blueprint”. 76.4% of patients (13/17) were responders (8/17 or 47% in remission) after 6 months of stimulation. Hamilton Rating Scale decreased 59.4%. Only one contact change was made in the first 6 months.

**Conclusions:** Prospective targeting using a connectome blueprint showed good clinical response and simpler management of stimulation parameters. Simplification of this essential and critical variable may contribute to improved trial design in future studies.

**Keywords:** Deep Brain Stimulation, Subcallosal Cingulate, TRD, Clinical Trials, Tractography

722. How Can We Optimize DBS Studies for Psychiatric Indications? New Data on Quality of Life and Personality

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1University Hospital, Bonn, Germany, 2University Hospital Freiburg, Germany
Background: Some DBS studies reported anecdotally a change in patients’ interpersonal behavior. This induced a debate if DBS can induce changes in personality. New data on personality and quality of life (QoL) from our DBS-TRD studies stimulating the superolateral forebrain bundle (slMFB) will be presented to demonstrate that in DBS studies, parameter beyond the scoring of symptoms might be meaningful.

Methods: 21 TRD patients were assessed before and six month after the onset of DBS. Personality was measured with the NEO-Five-Factor Inventory and with interviews with the patient and one relative; QoL was assessed with SF-36 and interviews. Baseline measures have been compared to DBS with t-tests, correlation analyses (with depression scores) have been performed with Pearson’s correlation coefficient (α = 5%).

Results: No change in any personality dimension from baseline to six months DBS was found. TRD Patients showed significant different scores on all five dimensions of personality at baseline. Lower scores in depression during DBS treatment were correlated with higher scores in extraversion. Overall, the closest relative judged the patients’ personality profile similar to the patients’ ratings. QoL was significantly ameliorated in patients with DBS but remained low overall.

Conclusions: DBS at the slMFB in TRD did not induce changes in personality itself, but the degree of antidepressant response was associated with higher extraversion. Although, QoL was ameliorated in the SF-36 score, interviews could add important dimensions of QoL. Personality and QoL seem to be important outcome parameters assessing the impact of DBS on a patient’s life beyond symptoms.

Keywords: Deep Brain Stimulation, treatment-resistant depression, Personality, Quality of Life, trial design

Methods: A de novo disruptive mutation in SLC39A13 was identified through whole exome sequencing of a sporadic trio from the Jerusalem Birth Cohort. Subsequently, cases from a NY sample were sequenced for the gene, based on TEC (38 genes) was performed with barcoded libraries (Nimblegen SeqCap EZ). Sequencing was done using an Illumina MiSeq sequencer followed by read alignment to hg19 and variant calling with GATK-UnifiedGenotyper. Variants were annotated by ANNOVAR and cross-referenced against 1000Genomes and ExAc databases.

Results: 10% of cases in the NY sample had novel or rare disruptive sequences of SLC39A13. They had the most severe phenotype in terms of cognition, negative symptoms and prefrontal developmental deficits based on NAA concentrations on MRS imaging. Cases with rare variants in the Zinc transporter and a family history had very young mothers. Early maternal age has also been associated with increased schizophrenia in offspring. Since Zinc is involved in the mechanisms that maintain cell cycle arrest in oocytes, mutations in zinc transporters be associated with early ovulation.

Conclusions: Zinc metabolism is an important candidate pathway for psychosis research and may present some ready treatment interventions for particular cases.

Supported By: This work was supported in part by the National Institutes of Health Grants NS21072 (MVC), MH086651 (MVC), RC1-MH088843 (DM), 5K24MH001699 (DM) and NYU CTSI UL1TR000038 (DM).

Keywords: zinc, neuroptrophin, epidemiology, mutation, variant

724. Rare Polymorphisms and Novel Mutations in the Neurotrophin Signaling Pathway Implicated in Schizophrenia Risk

Thorstien Kranz
NYU Langone Medical Center

Background: Neurotrophins demonstrate aberrant expression patterns in cortical areas of schizophrenia cases, however their mechanistic contribution to psychiatric disorders remains elusive. Targeted exome capture (TEC) was performed in neurotrophin genes in schizophrenia-related psychosis cases. We found rare missense-coding polymorphisms (MP) and novel variants (NV) in neurotrophin signaling pathway (NSP) genes. Some genes have a higher propensity to MPs. We suggest to consider MP/ NR in the NSP as susceptibility loci in schizophrenia.

Methods: Schizophrenia cases were diagnosed by: Diagnostic Interview for Genetic Studies, Family Interview for Genetic Study, Positive and Negative Syndrome Scale, Wechsler Adult Intelligence Scale and Early Trauma Inventory. TEC (38 genes) was performed with barcoded libraries (Nimblegen SeqCap EZ). Sequencing was done using an Illumina MiSeq sequencer followed by read alignments to hg19 and variant calling with GATK-UnifiedGenotyper. Variants were annotated by ANNOVAR and cross-referenced against 1000Genomes and ExAc databases.

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Conclusions: DBS at the slMFB in TRD did not induce changes in personality itself, but the degree of antidepressant response was associated with higher extraversion. Although, QoL was ameliorated in the SF-36 score, interviews could add important dimensions of QoL. Personality and QoL seem to be important outcome parameters assessing the impact of DBS on a patient’s life beyond symptoms.

Keywords: Deep Brain Stimulation, treatment-resistant depression, Personality, Quality of Life, trial design

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Conclusions: Zinc metabolism is an important candidate pathway for psychosis research and may present some ready treatment interventions for particular cases.

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**Results:** 37/48 cases harbored (MP) (MAF ≤ 1%) and (NV) in at least one gene. 7/48 cases showed novel variants in one gene of the neurotrophin signaling pathway. 80% of cases harboring MP and NR in the NSP displayed reduced verbal IQ (62–90) and 1/3 had learning disabilities. The highest burden was exhibited by the NTRK1-ARMS/Kidins220-TRIO pathway with >50% of all observed MP.

**Conclusions:** The NSP is affected in our schizophrenia-related psychosis cases. Accumulation of NV influences the pathophysiology of schizophrenia. Focusing on genetic vulnerability in genes with known mechanism and action will offer a promising starting point for further translational research in order to identify disease-relevant mechanisms.

**Supported By:** National Institutes of Health Grants NS21072 (MVC), MH086651 (MVC), RC1-MH088843 (DM), SK24MH001699 (DM) and NYU CTSI UL1TR000038 (DM). NS21072 (MVC), MH086651 (MVC), RC1-MH088843 (DM), ARMS, Sequencing

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**725. Behavioral, Neurophysiological and Synaptic Impairment in a Transgenic Neuregulin1 (NRG1-IV) Murine Schizophrenia Model**

Amanda Law

University of Colorado School of Medicine

**Background:** Neuregulin 1(NRG1), a trophic factor critical for synaptic development is associated with schizophrenia. The NRG1 gene undergoes extensive alternative splicing and to date little is known about the neurobiology of a novel NRG1 isoform, NRG1-IV, which is increased in the brain of individuals with schizophrenia and associated with genetic risk variation.

**Methods:** Here we developed a transgenic mouse model (NRG1-IV/NSE-tTA), whereby human NRG1-IV is selectively overexpressed in a neuronal specific manner and used a comprehensive molecular, biochemical, electrophysiological and behavioral screen. Furthermore, we investigated a signaling link between increased NRG1-IV and changes in the ErbB4, PI3K-AKT pathway, as seen in schizophrenia and whether abnormal neurobehaviors could be reversed via pharmacological inhibition of the pathway.

**Results:** Adult NRG1-IV/NSE-tTA mice exhibit abnormal behaviors relevant to schizophrenia, including impaired sensorimotor gating (F1,29=5.33, P<0.03), temporal order discrimination memory (t=2.97; df=25; p=0.007), spatial memory (t=2.902; df=15; p=0.01) and social behaviors. NRG1-IV altered the balance of cortical excitatory-inhibitory neurotransmission and decreased neuronal spine density (p<0.05) and dendritic development (p<0.01). Cortical ErbB4 and PIK3CD protein levels were increased, similar to findings in schizophrenia and PIK3CD inhibition, using IC87114, ameliorated behavioral deficits, including cognitive deficits dependent on mPFC and hippocampal function. Subjects N = range 7-20 per genotype.

**Conclusions:** These data demonstrate a novel role for NRG1-IV in learning, memory and neural circuit formation and a potential neurobiological mechanism for schizophrenia risk; demonstrate that deficits are pharmacologically reversible in adulthood and further highlight p110δ as a target for antipsychotic drug development. Developmental studies are currently underway.

**Supported By:** NIH P50 MH-086383-06, NIH R01 MH103716-02; NARSAD Young Investigator award. All to AJL. And NIMH Intramural Research Program, NIH

**Keywords:** Schizophrenia, Antipsychotics, Mouse model, NRG1, Animal Behavior

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**726. Predicting Relapse in Schizophrenia: Is BDNF a Plausible Biological Marker?**

Peter Buckley¹ and Anilkumar Pillai²

¹Medical College of Georgia at Augusta University, ²Medical College of Georgia

**Background:** Understanding the biological processes that underlie why patients relapse is an issue of fundamental importance to the detection and prevention of relapse in schizophrenia. Brain Derived Neurotrophic Factor (BDNF), a facilitator of brain plasticity, is reduced in patients with schizophrenia. In the present study, we examined whether decreases in plasma BDNF levels could be used as a biological predictor of relapse in schizophrenia.

**Methods:** 305 patients prospectively evaluated for relapse over 30 months in the Preventing Relapse in schizophrenia: Oral Antipsychotics Compared to Injectable: eValuating Efficacy (PROACTIVE) study. Serial plasma BDNF levels were measured in the samples by ELISA.

**Results:** Based on Receiver Operating Characteristic (ROC) curve analysis, 26% (18/70) of the subjects who experienced relapse were in the "low risk" group (BDNF values higher than the optimal cutpoint) and 28% (42/151) in the "high risk" group (BDNF values lower than the optimal cutpoint). There was no significant difference between the high risk and low risk groups in time to 1st relapse. In addition, no significant differences were found between the high risk [43% (23/53)] and low risk [35% (59/168)] groups in time to hospitalization [43% (23/53) vs 35% (59/168)] or exacerbation [22% (6/27) vs 18% (35/194)]. Regardless of treatment group (oral second generation antipsychotic vs long-acting injectable risperidone [43% (23/53) vs 35% (59/168)]), baseline BDNF value did not differ significantly between the high risk [43% (23/53)] and low risk [35% (59/168)] groups in time to hospitalization. BDNF values higher than the optimal cutpoint were predictive of relapse.

**Conclusions:** These results suggest that plasma BDNF does not predict relapse in schizophrenia.

**Supported By:** NIMH

**Keywords:** Relapse
727. Increased Levels of Kynurenic Acid Affect Human Developing Brain

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**Background:** Kynurenic acid (KYNA) is an intermediate metabolite of the kynurenine pathway and the only naturally occurring antagonist of N-methyl-D-aspartate receptor (NMDAR) in the human brain. Elevated levels of KYNA have been observed in pregnant women after viral infections and are considered to play a role in neurodevelopmental disorders. However, it is still unknown which developmental processes in the human brain are affected by elevated levels of KYNA.

**Methods:** To study the effect of KYNA on human cortical neurodevelopment, we used an in vitro system of multipotent cortical progenitors, i.e., radial glia cells (RGCs), enriched from human cerebral cortex at mid-gestation (16-19 gestational weeks).

**Results:** KYNA treatment via NMDAR antagonism significantly decreased proliferation and survival of RGCs. This alteration shifted the ratio of neurons to astrocytes, where number and activation of astrocytes increased while number of cortical progenitors and neurons decreased. Moreover, the balance of excitation vs. inhibition was affected. KYNA treatment reduced differentiation of RGCs into GABAergic neurons, while the number of glutamatergic neurons was relatively spared. Notably, in mixed cortical cultures KYNA induced an inflammatory response as evidenced by increased levels of the pro-inflammatory cytokine interleukin 6.

**Conclusions:** Elevated levels of KYNA in vitro play a significant role in determination of human RGCs fate. KYNA antagonized NMDARs and activated an inflammatory response, which resulted in altered differentiation of cortical progenitors. These changes suggest a mechanism for impairment of cortical circuitry formation in the fetal brain after viral infection, as seen in neurodevelopmental disorders such as schizophrenia.

**Supported By:** NIH R01 MH094328

**Keywords:** Fetal Development, NMDA antagonists, interneurons, Schizophrenia, Kynurenic acid

728. Deficits in Complex MMN to Group Size Deviance in First-Episode Schizophrenia-Spectrum Psychosis

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¹University of Pittsburgh Medical Center, ²University of Pittsburgh

**Background:** Individuals with long-term schizophrenia (SZ) show reductions in simple mismatch negativity (MMN) to infrequent stimulus parameter deviance, and in complex MMN to infrequent pattern deviance. First episode schizophrenia-spectrum individuals (FE) show less reduction of simple MMN. Complex pattern deviance may be more suitable for elucidating subtle deficits in auditory perception at first-episode, and may be a useful biomarker for the presence of schizophrenia.

**Methods:** We measured simple MMN to pitch and duration deviants, and complex MMN to an extra fourth tone amongst standard groups of three tones (1 kHz, 50 ms duration, 5 ms rise/fall, 80 dB, 330 ms SOA, 800 ms ITI) in 24 SZ, and 23 matched healthy controls (HCSZ), and in 24 FE (within 6 months of first-episode), and 23 matched healthy controls (HCFE).

**Results:** For simple MMN, SZ showed reductions in pitch (p < .001) and duration (p < .008), and for complex MMN (p = .043). Simple MMN was not significantly reduced in FE (pitch p = .215, duration (p = .705), but complex MMN was (p = .003).

**Conclusions:** Both simple MMN and complex MMN are impaired in long-term schizophrenia, whilst only complex MMN was impaired in FE; simple MMN was not impaired at first break. Thus, complex MMN may be a more sensitive biomarker of the presence of schizophrenia early in disease course. To assess whether complex MMN has greater sensitivity to detect incipient psychosis, both simple MMN and complex MMN will be measured in prodromal individuals.

**Supported By:** NIH R01 MH094328

**Keywords:** Mismatch Negativity, Schizophrenia, first-episode, Grouping


Keisuke Takahata¹, Yoshiyuki Kimura², Hitoshi Shimada¹, Masanori Ichise¹, Hajime Tabuchi², Soichiro Kitamura¹, Manabu Kubota¹, Sho Moriguchi¹, Tatsuya Ishii¹, Fumitoshi Nishii¹, Hironobu Endo³, Yoko Morimoto⁴, Michitaka Funayama⁵, Matsumoto Onaya⁶, Naruhiko Sahara¹, Satoshi Umeda⁷, Masaru Mimura³, Makoto Higuchi³, and Tetsuya Suhara¹

¹National Institute of Radiological Sciences, ²National Center for Geriatrics and Gerontology, ³Keio University School of Medicine, ⁴Kyoto Prefectural University of Medicine, ⁵Kobe University Graduate School of Medicine, ⁶Tokyo Dental College Ishikawa General Hospital, ⁷Ashikaga Red Cross Society Hospital, ⁸National Hospital Organization Shimofusa Psychiatric Medical Center, ⁹Keio University

**Background:** Schizophrenia-like psychosis is common among patients with traumatic brain injury (TBI). Neuropathological studies have shown that abnormal tau and amyloid accumulations were found in the brains of single-severe TBI patients. These pathologies may be involved in the development of post-TBI psychosis, in light of the fact that the occurrence of psychosis after injuries is typically delayed-onset. To examine this notion, we evaluated tau and amyloid depositions in single-severe TBI patients with or without psychosis using positron emission tomography (PET).

**Methods:** PET imaging of tau and amyloid lesions were performed with [11C]PBB3 and [11C]PiB, respectively, for 14 TBI patients (45.6 ± 10.8 y) with (n = 6) or without (n = 8) psychosis and 15 age-matched normal controls. [11C]PBB3 binding capacity [cm3] was calculated as a sum of radioligand binding potential voxel values above a threshold in a target area.
region times the voxel volume. [11C]PiB-PET images were assessed by visual inspection. Severity of symptoms was evaluated with BPRS, CES-D and Apathy Scale.

**Results:** Mean interval between the onset of psychosis and TBI was 3.7 ± 1.8 years. ANCOVA with age as a covariate revealed that TBI patients with psychosis showed higher [11C]PBB3 binding capacities in the neocortex than those without psychosis and healthy controls. Furthermore, [11C]PBB3 binding capacity in the gray matter correlated with severity of psychosis. None of patients and healthy controls were [11C]PiB-positive.

**Conclusions:** Our findings indicate that the onset and progression of psychosis at a late stage after TBI is intimately associated with tau pathology rather than -amyloid depositions.

**Supported By:** JSPS, AMED

**Keywords:** Traumatic Brain Injury, Tau Imaging, Amyloid imaging, Post-traumatic psychosis, Positron emission tomography

**730. Structural and Functional Connectivity in Adolescent Psychosis**

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1University of California, Los Angeles, 2Feinstein Institute for Medical Research, 3The Zucker Hillside Hospital

**Background:** Executive function deficits and corresponding changes in the structure and function of the central executive network (CEN) are well established in schizophrenia. However, beyond schizophrenia, executive dysfunction across the psychosis spectrum is less well understood. Here, we examined the neural basis of executive deficits in youth with a range of psychotic spectrum disorders.

**Methods:** 51 individuals (age 14-23) with diagnoses across the psychosis spectrum (schizophrenia, schizoaffective, psychosis NOS, MDD with psychosis, bipolar with psychosis), and 53 age matched unaffected controls participated in the Multimodal Evaluation of Neurodevelopmental Disorders (MEND) study, which included multimodal neuroimaging, cognitive testing, and clinical interviews.

**Results:** Even in a sample with a wide range of symptoms, we found multimodal disruptions in the CEN. Behaviorally, patients showed impaired working memory (WM) performance, which correlated with the level of positive symptoms. We then probed structural and functional connectivity of networks supporting WM. Resting state fMRI revealed altered functional connectivity in patients between the CEN and another large scale intrinsic brain network, the salience network. Diffusion tensor imaging revealed decreased white matter integrity (structural connectivity) in the superior longitudinal fasciculus, the main fronto-parietal connection, in patients.

**Conclusions:** Our evidence supports disruptions in the structure and function of the CEN in young individuals with early stage psychotic spectrum disorders. Furthermore, across individuals with a range of symptoms and illness types, WM deficits scaled with severity of psychotic symptoms, potentially indicating a specificity for psychosis. Thus, CEN function and WM performance should considered not just as schizophrenia endophenotypes but as broader markers of psychosis.

**Supported By:** R01 MH101506

**Keywords:** Schizophrenia, Neurodevelopment, Adolescents, Brain Imaging, Connectivity

**731. Biomarkers of Genetic and Environmental Psychosis Risk: Dopamine and Glutamate Imaging**

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1CSC Hammersmith Hospital and Institute of Psychiatry, 2CSC Hammersmith Hospital

**Background:** People with the 22q11.2 deletion have a 30 fold increased risk of psychosis. The deletion affects genes involved in dopamine and glutamate regulation, as well as a number of other genes. Environmental risk factors, including early life adversity, migration and life events increase the risk of psychosis. However it is not known whether these genetic and environmental risk factors translate into altered dopaminergic and glutamatergic function in vivo.

**Methods:** The study recruited one hundred volunteers, comprising asymptomatic, drug naïve young carriers of the 22q11.2 deletion who had not developed psychosis, drug naïve patients in their first episode of psychosis, people with environmental risk factors for psychosis and matched healthy controls. They all received PET imaging with 18F-DOPA to give Ki (dopamine synthesis capacity), MRS of glutamate levels, and clinical measures.

**Results:** Ki was elevated in both the 22q11.2 group (cohen’s d = 1.1, p < 0.01), and first episode group (cohen’s d = 1.2, p < 0.01) relative to controls. In contrast Ki was significantly reduced in the people at environmental risk of psychosis (effect size d = 0.7, p < 0.05). There was no significant difference in Ki between 22q11.2 carriers and first episode patients (p > 0.2), or in glutamate levels in any group. However Ki was inversely correlated with glutamate levels (r = 0.5, p < 0.05). To date one of the 22q11.2 group has gone on to develop schizophrenia.

**Conclusions:** These data indicate that dopamine synthesis capacity, but not glutamate, is a trait marker for genetic psychosis risk, and predate the development of clinical symptoms, but is not a marker for environmental risk factors for psychosis.

**Supported By:** MRC

**Keywords:** Genetics, Brain Imaging, Dopamine, Glutamate, At-Risk Youth

**732. Individual Differences in the Healthy Population Helps Identify Schizophrenia-Specific Disruptions in Resting State Networks Related to Cognitive Control**

Amanda Rodrigue, David J Schaeffer, Brett A Clementz, and Jennifer E McDowell

University of Georgia

**Background:** Cognitive control deficits in schizophrenia (SZ) have been attributed to alterations in prefrontal cortex functional connectivity (as measured by rsfMRI) with executive control (ECN) and default mode (DMN) networks.
Healthy comparison groups, however, often have superior cognitive control, meaning differences between groups could be due to poor cognition rather than the presence of a schizophrenia diagnosis. This study used two comparison groups: one with high cognitive control (HCC) and one with low cognitive control (LCC). Using both healthy comparison groups would identify schizophrenia-specific connectivity disruptions (distinctions between SZ and both LCC and HCC groups) and provide a clearer picture of connectivity disruptions underlying poor cognitive control in general.

**Methods:** HCC (N = 28), LCC (N = 30), and SZ (N = 31) individuals underwent rsfMRI. The ECN and DMN resting state networks (RSNs) were identified with a group-wise probabilistic independent component analysis (pICA). pICA results were fed into FSL’s dual regression to quantify voxel-wise connectivity with the RSNs of interest. One-way ANOVAs were conducted for each network.

**Results:** Differences in ECN and DMN connectivity were mostly graded (HCC > LCC > SZ or HCC < LCC < SZ) indicating a quantitative rather than qualitative difference in network connectivity. LCC and SZ groups exhibited weaker connections among regions involved in or related to the RSN of interest and less differentiation between unrelated regions and the RSN of interest.

**Conclusions:** Connectivity mechanisms underlying poor cognitive control do not seem to be different between healthy people with LCC and individuals with schizophrenia, although individuals with schizophrenia tend to have more severe connectivity disruptions in the ECN and DMN.

**Supported By:** NIMH

**Keywords:** Schizophrenia, cognitive control, Resting state fMRI, Individual differences

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**733. Genetic Determinants of Working Memory: A High-Throughput Voxel-Wise GWAS Approach**

**Daniela DeAlbuquerque**1, Michael Gregory2, Daniel Weinberger3, Karen Berman2, and Joseph Callicott4

1NIMH, 2CNB, NIMH, NIH, 3Leiber Institute for Brain Development, 4CTNB, NIMH, NIH

**Background:** Working memory functioning is necessary for healthy cognition and is impaired in neuropsychiatric disease, including schizophrenia. Though this functioning has been shown to be genetically-mediated, no comprehensive exploration for genetic associations has been undertaken. We tested for genetic underpinnings of working memory functioning using a high-throughput, voxel-wise GWAS approach.

**Methods:** N-back fMRI and Illumina genome-wide microarray SNP data from 501 healthy adults were collected. After preprocessing, 2back-vs-1back BOLD activations from each brain voxel were used as quantitative phenotypes in GWAS analyses after residualizing for age, sex and performance. Bonferroni correction for multiple comparisons was employed to account for the number of linkage-independent SNPs and the number of resolution elements in the imaging data (p-uncorrected <3.33x10^-11). We sought to replicate the significant results in the independent Philadelphia Neurodevelopment Cohort (n=341 children) using identical methodology.

**Results:** We found significant association between working memory functioning of the left DLPFC (BA9) and an LD-block on chromosome 8 (peak=rs36111028, p=3.12x10^-11). This finding replicated in the PNC sample, showing significant association of this SNP with the same region of left DLPFC (BA9; p = 0.004).

**Conclusions:** Here, we identified and replicated significant association of rs36111028 with working memory-related functioning of the left DLPFC (BA9) using a whole-brain, genome-wide, data-driven approach. The KCNV1 gene, just centromeric to this locus, is highly expressed in cortex and contains one of the 108 PGC-implicated loci in schizophrenia. Both the functional significance of KCNV1 and the critical role of the DLPFC to working memory and schizophrenia support the feasibility of this novel voxel-wise, genome-wide methodology.

**Supported By:** NIMH

**Keywords:** Working Memory, Schizophrenia, Genome-Wide Association Study, Functional MRI, High-Throughput

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**734. Aversive Conditioning Responses in the Psychosis Prodome: An ERP Study**

**Anna Watters,** Petra Rupert, Daniel Wolf, Monica E. Calkins, Ruben C. Gur, Raquel E. Gur, and Bruce Turetsky

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**Background:** Social cognition and emotional processing are compromised in schizophrenia. Disruptions in these domains, while often associated with chronic negative symptoms, may also be present during the prodromal at-risk state. Aversive conditioning is an established translational research paradigm to investigate affective reactivity and learning. Using an aversive conditioning ERP paradigm with social cues, we investigated whether schizophrenia patients and at-risk youths differentially respond to aversively conditioned faces.

**Methods:** Participants (ages 10-30) were enrolled into three demographically matched groups: clinical risk for psychosis (CR, n=32), schizophrenia (SCZ, n=26), and healthy control (HC, n=31). EEGs were recorded during a delay aversive conditioning task in which three neutral faces were paired with an aversive tone at 100%, 50% and 0% contingencies. Analysis focused on group differences in ERP peaks representing visual processing (occipital P120), emotional valence (frontal VPP), and directed attention (parietal-occipital P300) for dimensions of Aversiveness (100% vs 0%) and Uncertainty (50% vs 100% + 0%).

**Results:** HC, but not CR or SCZ, showed increased P300 amplitude to Aversively vs. Nonaversively conditioned stimuli. In SCZs, this failure was associated with greater negative symptoms. CR, but not SCZ or HC, showed increased VPP amplitude to Uncertainly Aversive stimuli.

**Conclusions:** SCZ and CR both fail to allocate appropriate salience to social cues that are predictably aversive. CR, but not SCZ exhibit heightened emotional reactivity to social cues that are of uncertain salience. Clinical risk may involve neural abnormalities distinct from both healthy and fully-established disease states.

**Supported By:** Conte Study Grant
735. The Contribution of Major Depressive Disorder Risk Alleles to Youth depression: Does Stratifying by Co-Occurring Conduct Problems Refine the Phenotype?

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Background: Depression is a complex, heterogeneous multifactorial disorder. Family, twin and longitudinal studies of depression suggest that in youth, conduct disorder may be an important clinical indicator of depression heterogeneity. Depression without conduct disorder presents more similarly to adult depression compared to depression with conduct disorder. We used polygenic risk scores (PRS) derived from a patient discovery sample of adults with MDD (major depressive disorder) as indicators of depression genetic liability to test the hypothesis that MDD PRS are associated with child/adolescent depression only when the phenotype is refined by excluding depressed individuals with co-occurring conduct problems.

Methods: Data were primarily analyzed using regression-based analyses in a UK, prospective, population-based cohort (ALSPAC). The sample included individuals with depression data (Mood and Feelings Questionnaire cut-point) in childhood (age 9, parent-report, N=7977) and in adolescence (age 16, self-report, N=5595). PRS were derived from a published Psychiatric Genomics Consortium genome-wide association study of MDD.

Results: MDD PRS were not associated with youth depression when including all depressed cases (childhood: OR=1.11, 95% CI 0.94-1.31, N=2343; adolescence: OR=1.09, 95% CI 0.99-1.20, N=2685) but were associated with depression when excluding cases with co-occurring conduct problems (childhood: OR=1.30, 95% CI 1.05-1.61, N=2277; adolescence: OR=1.11, 95% CI 1.00-1.23, N=2633).

Conclusions: Our findings suggest that depression genetic liability, indexed by MDD PRS, is associated with depression in children/adolescents but only when it does not co-occur with conduct problems. This finding requires replication but further suggests that in young people, conduct problems might be a useful way to stratify depression.

Supported By: Medical Research Council

Keywords: Depression, Childhood, Adolescence, Genetics, Polygenic Risk Score

736. Attachment Insecurity and DNA Methylation in Risk for Postpartum Depression

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Background: Postpartum depression (PPD) is common and debilitating. Predisposing factors and clinical phenotypes in PPD differ from those of depression in other life periods; thus, distinct psychobiological pathways may underlie PPD. Previous work by ourselves and others has established adult attachment insecurity as a potent predictor of postpartum depression. We wished to establish whether epigenetic correlates of attachment insecurity exist, and to determine whether these could be useful for the prediction of PPD.

Methods: Psychiatric evaluation, attachment score, and buccal swabs were obtained from 41 healthy pregnant women. DNA methylation patterns were analyzed by Nimblegen Capture bisulfite sequencing. Depressive symptoms were evaluated on a monthly basis for six months postpartum.

Results: Preliminary analysis of methylation patterns within three candidate genes among 16 subjects with initially available data revealed a region of the oxytocin receptor gene (OXTR) where seven contiguous individual CpG loci were highly correlated (p<0.05) with attachment insecurity.

Conclusions: Attachment insecurity is a major factor predisposing to postpartum depression. Methylation at key genetic loci may be related to attachment insecurity, representing an important biological mechanism linking early life stress, personality characteristics, and psychiatric diatheses.

Supported By: NARSAD 2014 Young Investigator grant

Keywords: Epigenetics, Postpartum Depression, attachment, DNA methylation

737. High Stress in Pregnant Mothers is Associated with Reduced Global Brain Efficiency in the Fetus

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Background: Maternal prenatal stress has detrimental and lasting effects on children’s neurobehavioral health. Harmful effects to the child are thought to be transferred through the intrauterine environment, but human data to support this is lacking. It is difficult to disentangle shared influences of pre- and postnatal rearing environments in reconciling the origins of problem behavior, as these are highly interrelated. Advances in fetal functional connectivity MRI (fcMRI) make it possible to examine the human connectome before
Methods: We examined the effect of stress on fetal brain development in N=47 pregnant women. Using maternal self-report measures and fetal fcMRI, we addressed the primary hypothesis that fetal neural functional connectivity is related to maternal stress. Associations between variables were tested in multilevel regression models that included age and motion as covariates.

Results: Scales from six questionnaires assessing maternal stress were best represented as single latent factor, showing high loadings and good model fit ($\chi^2$=19.11, df=9, $p=0.02$; CFI=.97; TLI=.96; RMSEA=.08). Maternal stress, represented as a single latent factor, was related to fetal neural connectivity. Specifically, higher maternal prenatal stress was associated with reduced strength of neural efficiency ($B=-.007$, $SE=.003$, $\beta=.24$, $p=.04$).

Conclusions: For the first time, we report that maternal prenatal stress exerts intrauterine programming of in vivo human neural functional networks. This discovery has implications for transfer of risk via early brain programming, which may be relevant to long-term psychiatric health.

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Keywords: Fetal programming, Brain connectivity, Functional MRI, Pregnancy, Resting State

738. Evidence from Gene-Environment Mouse Models that Amygdala Oligodendropathy Contributes to Emotional Pathology

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Background: Oligodendrocyte (OL) function, most notably myelination, is essential for efficient functional connectivity within and between neurocircuits. In depression, expression of OL genes and proteins is attenuated, including in the amygdala. The aim of the present mouse study was to elucidate the role of oligodendrocytes in mediating stress-induced emotional pathologies.

Methods: Firstly, RNA-sequencing of the amygdala transcriptome and subsequent gene expression deconvolution (GED) analysis of these data were performed in mice that received 15 days of chronic social stress (CSS) and controls (CON). Based on these findings, a genetic mouse model of compromised OL function in terms of hemizygosity of the OL gene cyclic nucleotide phosphodiesterase (Cnp1) was utilised in a 2 genotype (G) (WT, Cnp1 +/-) x 2 environment (E) (CSS, CON) design, to study GxE effects on emotional behavior (social approach test, Pavlovian fear conditioning) and amygdala microglia activation (iba-1 protein immunohistochemistry).

Results: CSS resulted in reduced expression of a number of OL-enriched genes in amygdala tissue and GED identified a decreased proportion of OLs in CSS mice. Interestingly, sociosexual motivation was reduced in Cnp1 +/- x CSS mice specifically; Cnp1 +/- x CON mice exhibited impaired memory but Cnp1 +/- x CSS mice nonetheless exhibited robust fear learning and memory. Iba-1 immunohistochemical analysis showed additive effects of GxE with microglia activation lowest in WT x CON and highest in Cnp1 +/- x CSS mice.

Conclusions: This mouse-model study provides descriptive ExG and causal GxE evidence that reduced amygdala OL function is associated with inflammation and contributes to the pathophysiology via which CSS leads to emotional psychopathology.

Supported By: Swiss National Science Foundation (grant 31003A_160147)

Keywords: social stress, oligodendrocytes, RNA-sequencing, inflammation, microglia

739. Multivariate Investigation of Brain and Behavioral Outcomes in Individuals with FMR1 Full Mutation

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Background: Fragile X syndrome (FXS), with a known single gene etiology, is an important model for understanding the biological basis of cognitive and behavioral phenotypes. We present the first multivariate investigation of the relationship between levels of the fragile X mental retardation protein (FMRP), brain structure and behavioral outcomes in females with FXS who have a broader range of symptoms and more variation in FMRP levels relative to males.

Methods: Participants included 30 females with FXS (age 11-23) who completed MRI and assessments of IQ, executive function and verbal fluency. Support vector regression (SVR) was used to create a multivariate model explaining the relationship between FMRP percentage and regional brain volumes while controlling for age and IQ. Correlations between regions that were highlighted in the model and cognitive performance we re-explored.

Results: The SVR model ($R = 0.44$) indicated that FMRP influenced variation in regional brain volume positively. The pattern of regional contribution to the model highlighted the influence of FMRP on cortical regions including bilateral cingulate gyri, bilateral frontal and temporal lobes and right
supramarginal gyrus. Volumes of bilateral parahippocampal and right inferior frontal gyri were associated positively with executive function and verbal fluency scores, respectively.

Conclusions: These results demonstrate the effects of FMRP on variation in brain volume measured in females with FXS during adolescence/young adulthood. FMRP levels impacted specific frontal, temporal and parietal regions more profoundly than others. Brain volume/cognition correlations suggest that neuroanatomical metrics could represent an intermediate phenotype between deficient FMRP and cognitive function.

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Keywords: multivariate analysis, Structural MRI, Machine learning, Executive Function, brain development

740. Prenatal Stress Alters Intraterine Environment and Contributes to Adult Microbiome and Behavioral Changes

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Background: Recent studies demonstrate that exposure to stress changes the composition of the intestinal microbiota. Maternal stress during pregnancy has been linked with psychiatric disorders. In this study we address the contribution of maternal stress and commensal microbes on the development of adult psychopathology.

Methods: Pregnant C57/BL6 females were assigned to stress or non-stressed control group (n=14/group). The stressed group were restrained between embryonic day (E) 10-E16. Placentas and amniotic fluid were collected from a cohort of pregnant females at E17.5. Microbial diversity was assessed using the Illumina MiSeq platform, for targeted 16S ribosomal RNA gene sequencing. RT-PCR was used to examine gene expression. Offspring behavior was assessed in adulthood.

Results: Prenatal stress leads to alterations in the maternal and offspring intestinal microbial populations (p<0.05), and alterations in the placental microbes, which did not reach statistical significance (p=0.08). Female placentas and fetal brains demonstrated increased IL-1beta (p<0.05) and decreased BDNF (p<0.05). In the adult female offspring alterations in cognition in the novelty object recognition task (p<0.05) and anxiety-like behavior in the elevated plus maze (p<0.05) were associated with increased amygdala gene expression of IL-1beta but the difference was not quite statistically significant (p=0.09) and decrease in BDNF (p<0.05). In the male offspring prenatal stress lead to decreased social interaction (p<0.05) and a distinct pattern of gene expression than that found in females.

Conclusions: Gestation is a critical window in contributing to the development of adult psychopathology, and the microbiome may be an important link between early life environment and later life behavioral changes.

Supported By: NARSAD Young Investigator Award, KL2TR001068, March of Dimes Transdisciplinary Scholar

Keywords: prenatal maternal stress, Microbiome, Anxiety, Cytokines and Chemokines, BDNF

741. Hippocampal Mitochondrial Gene Expression Changes with Development and Early Life Stress

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Background: Early life stress (ELS) impacts over 3.4 million American children and increases psychiatric disorder risk. In mice, ELS accelerates hippocampal maturation, leads to precocious fear learning, and elevates anxiety and depressive-like behaviors, suggesting ELS-associated hippocampal changes may impact psychopathology risk. Mitochondria play a vital role in neuronal differentiation and maturation; however, no studies have examined normative or ELS effects on hippocampal mitochondrial gene expression over early development. We hypothesize that ELS will alter the developmental profile of mitochondrial gene expression, and possibly contribute to risk for negative developmental outcomes.

Methods: For ELS, C57BL/6N mice were reared with restricted access to bedding from p4-p11. Timepoints prior to (p4), immediately after ELS (p12), and into adulthood (p16, p21, p28, p38, p50) were examined. Hippocampal samples (n=3-6/timepoint) 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. Expression was calculated based on individual plate standard curves; developmental and between-group differences were examined using two-way ANOVA.

Results: Mitochondrial gene expression increased with development (p’s<.0001). Across development, ELS significantly reduced expression of four mitochondrial genes (p’s<.05) and neared significance for three additional genes (p’s<0.1). Age by ELS interaction neared significance for seven genes (p’s<0.1).

Conclusions: This is the first study examining mitochondrial gene expression during murine hippocampal development. These results suggest that ELS may alter ontogeny of mitochondrial gene expression, with implications for understanding ELS effects on hippocampal development.

Supported By: R25 MH101076

Keywords: Brain Development and Aging, Early Life Stress, Psychopathology, Mitochondria

742. Gut Microbiome and Brain Functional Connectivity in Infants: A Preliminary Study Focusing on the Amygdala

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Background: Prenatal stress leads to alterations in the maternal and fetal microbiome, which may impact brain development and later life functional connectivity. This is the first study to examine the effects of early life stress on functional connectivity in the infant brain.

Methods: Infants were recruited from a cohort of pregnant females at E17.5. Microbial diversity was assessed using the Illumina MiSeq platform, for targeted 16S ribosomal RNA gene sequencing. RT-PCR was used to examine gene expression. Offspring behavior was assessed in adulthood.

Results: Prenatal stress leads to alterations in the maternal and offspring intestinal microbial populations (p<0.05), and alterations in the placental microbes, which did not reach statistical significance (p=0.08). Female placentas and fetal brains demonstrated increased IL-1beta (p<0.05) and decreased BDNF (p<0.05). In the adult female offspring alterations in cognition in the novelty object recognition task (p<0.05) and anxiety-like behavior in the elevated plus maze (p<0.05) were associated with increased amygdala gene expression of IL-1beta but the difference was not quite statistically significant (p=0.09) and decrease in BDNF (p<0.05). In the male offspring prenatal stress lead to decreased social interaction (p<0.05) and a distinct pattern of gene expression than that found in females.

Conclusions: Gestation is a critical window in contributing to the development of adult psychopathology, and the microbiome may be an important link between early life environment and later life behavioral changes.

Supported By: NARSAD Young Investigator Award, KL2TR001068, March of Dimes Transdisciplinary Scholar

Keywords: prenatal maternal stress, Microbiome, Anxiety, Cytokines and Chemokines, BDNF
Aging in Schizophrenia

Background: There has been a recent surge of interest in the possibility that the gut microbiome influence brain development and associated risks for mental disorders. However, to date, there have been no studies on the relationship between the gut microbiome and functional brain organization during human infancy.

Methods: Resting-state functional magnetic resonance imaging (rsfMRI) was conducted on 39 1-year-old infants who had donated fecal samples for the identification and quantification of bacterial taxa (i.e. enterostate, alpha diversity). Seed-based functional connectivity analysis centered on the amygdala was first conducted given its high relevance in emotional/social behaviors that are documented to be mostly affected by gut microbiome. Independent component analysis (ICA) was also conducted to explore potential network-level effects.

Results: Functional connectivity between the right amygdala and bilateral anterior insula significantly (cluster-level P<0.05) differed across three infant groups characterized by distinct microbiome compositions (E1-E3). Consistently, two functional networks overlapped on the detected anterior insula clusters and demonstrated similar profiles across the three groups. Importantly, the interaction strength between the two networks significantly predicted performance on the Mullen scales at 2 years of age (r = -0.51, P = 0.0036). In addition, there was a superior temporal cluster showing significant connectivity differences with the left amygdala and two other clusters showing significant correlations with alpha diversity.

Conclusions: We have demonstrated associations between infant gut microbiome and amygdala-insula functional connectivity, as well as related functional networks and behavior. Future studies should determine whether microbiome-associated changes in neurocircuitry influence later risk for psychopathology, particularly in the realm of anxiety-related behaviors.

Supported By: R33MH1104330
Keywords: Gut Microbiome, Resting state fMRI, Infants, Amygdala, Insula

47. Gut Microbiome, Resting state fMRI, Infants, Amygdala, Insula

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Supported By: National Institute of Mental Health (MH112168)
Keywords: Gut Microbiome, Resting state fMRI, Infants, Amygdala, Insula

744. Linking Macroscale Connectivity Disruptions with Microscale Measures of Spine Density and Gene Expression

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Background: Schizophrenia is well known to involve changes at both the microscale cellular and macroscale level of brain connectivity. At the cellular microscale, schizophrenia has been reported to include pronounced reductions in pyramidal spine density. In parallel, at the macroscale whole-brain level MRI studies have reported disruptions in structural and functional connectivity networks and connectome organization. Heritability and GWAS studies have further shown a strong genetic component of both effects. Here, I will discuss findings of changes at different levels of brain connectivity to be related

Methods: Changes in microscale spine density as collated from 20+ studies using Golgi staining in post-mortem material were

SYMPOSIUM
Disease Connectomics: From Gene Expression to Large-Scale Brain Networks
Saturday, May 20, 2017 - 3:00 PM - 5:00 PM
Sapphire AB
Chair: Andrew Zalesky
Co-Chair: Christos Pantelis

743. Brain Network Resilience and Accelerated Brain Aging in Schizophrenia
Andrew Zalesky1, Vanessa Cropley1, Paul Klauzer2, Christos Pantelis1, and ASRB Working Group3

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Background: Age-related trajectories of gray matter and white matter changes in schizophrenia remain unclear. We sought to measure whether these changes remain stable, are accelerated, or are diminished with age. We also sought to examine whether brain networks in schizophrenia are resilient to any accelerated changes associated with aging.

Methods: Gray matter volume, fractional anisotropy and whole-brain white matter networks were mapped in 326 individuals diagnosed with schizophrenia and in 197 healthy comparison subjects of age 20–65 years. Polynomial regression was used to model the influence of age on gray matter volume and fractional anisotropy at a whole-brain and voxel level. Brain network resilience was measured within each network module and compared between patients and controls using permutation testing.

Results: While more than 50% of cortico-cortical and cortico-subcortical white matter fiber bundles were disrupted in schizophrenia, network modules were more resilient to these disruptions in patients compared to healthy comparison subjects. Significant loss of gray matter volume was evident in schizophrenia, progressively worsening with age to a maximal loss of 8% in the seventh decade of life. The inferred rate of gray matter volume loss was significantly accelerated in schizophrenia up to middle age and plateaued thereafter. In contrast, significant reductions in fractional anisotropy emerged in schizophrenia only after age 35.

Conclusions: The findings suggest that schizophrenia is characterized by an initial, rapid rate of gray matter loss that slows in middle life, followed by the emergence of a deficit in white matter that progressively worsens with age at a constant rate.

Supported By: National Health and Medical Research Council of Australia
Keywords: Schizophrenia, Resilience, Brain Aging, Connectivity, Diffusion Tensor Imaging (DTI)
correlated to patterns of cortical changes in macroscale connectivity as measured by means of diffusion MRI (n=40+ controls/patients, 3Tesla, 1.5T replication set). Second, the pattern of macroscale cortical connectivity was cross-correlated to the cortical pattern of expression of schizophrenia risk genes as selected by the GWAS study of the PGC with expression data derived from the Allen Human Brain Atlas (AHBA).

**Results:** The pattern of changes in spine density across cortical areas was significantly correlated to the pattern of changes in macroscale MRI connectivity. Second, the pattern of AHBA expression of PGC risk-genes significantly correlated to the pattern of macroscale brain connectivity as observed in the patient population. These findings were found to be disease specific, with differentiating effects observed in a population of bipolar patients (n=100+ patients, 3 Tesla, Diffusion MRI).

**Conclusions:** Our findings show genetic, microscale, and macroscale changes of brain connectivity in schizophrenia to be related.

**Supported By:** MQ, NWO VIDI

**Keywords:** Connectivity, Schizophrenia, dendritic spine, Gene Expression, connectome

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**745. Using Brain Stimulation to Probe Network Pathology and Reverse Brain Dysfunction**

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**Background:** Psychiatric disorders are characterised by selective deregulation in the activity of local brain regions as well as macroscopic brain networks. The neural mechanisms that link altered activity in specialised regions with the emergence of large-scale brain network pathology remain unknown. This knowledge is essential to understand the genesis and evolution of network pathology, as well as guide new therapeutic interventions aiming to reverse brain dysfunction, such as transcranial magnetic stimulation (TMS).

**Methods:** I will describe the results of empirical and computational studies that have aimed to unfold the neural principles that underpin the emergence of brain network pathology following local deregulations. In these studies we used neuroimaging, brain stimulation, network science and computational modelling. I will also describe how knowledge gathered from this work can be translated to clinical investigations.

**Results:** I will discuss the results from multimodal investigations, showing that the effects of local neural perturbations on large-scale neural dynamics may reflect a fast-slow timescale hierarchy from periphery to core brain regions. These results highlight that the temporal organisation of the brain may explain the selective effect of localised neural pathology in the brain network. I will conclude by showing how this knowledge may be used to guide targeted TMS interventions for connectome pathologies.

**Conclusions:** Our work highlights novel neural mechanisms supporting the selective effect of a local neural perturbation to whole-brain network dynamics. The use of this knowledge has the potential to increase the efficacy of TMS as a tool to restore brain network dysfunctions and improve symptoms of psychiatric disorders.

**Supported By:** National Health and Medical Research Council (APP1099082)

**Keywords:** connectomics, Brain networks, Brain Stimulation, Brain Imaging, TMS

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**746. Relating Individual Differences in Functional Brain Connectivity to Trait-Level Paranoia and Delusional Thinking**

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**Background:** Delusions are fixed false beliefs. Most commonly, they take on a persecutory/paranoid theme, in which patients believe that something or someone is conspiring against them. While delusions are a hallmark symptom of schizophrenia and other psychotic illness, paranoia follows a spectrum from normality to pathology in the general population. However, the neural correlates of individual differences in trait-level paranoia are not well understood.

**Methods:** We developed a long-form narrative describing a complex social scenario that is deliberately ambiguous with respect to characters’ trustworthiness and intentions. Pilot studies confirmed that this narrative evoked a range of interpretations across subjects, from less suspicious to more so. Healthy subjects on a range of trait-level paranoia (n=20+) listened to the narrative during fMRI scanning, and their subsequent feelings and beliefs about the narrative were characterized with an extensive debriefing questionnaire. Subjects were also scanned at rest.

**Results:** I will demonstrate how specific brain circuits underlie both trait-level paranoia (as measured with clinical scales) and state-level paranoia (as measured by behavioral response to the narrative). Results will link (1) functional connectivity/activation during narrative listening, (2) functional connectivity at rest, and (3) suspicious belief formation, showing how patterns of brain activity relate to subsequent interpretation of the narrative. Consistencies and differences across subjects will be discussed.

**Conclusions:** This work combines an innovative naturalistic task with traditional rest to probe the brain networks underpinning paranoia. In addition to advancing our understanding of the biology of paranoia, this work could help identify those with or at risk for delusional thinking.

**Keywords:** Individual differences, Schizophrenia, paranoid threat, delusions, Functional connectivity
747. Verbal Learning and Memory in PTSD and TBI: Relation to Functional Outcomes

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Background: Given the high correspondence between mild TBI (mTBI) and psychiatric symptoms, it is important to disentangle the impact of these conditions. Extant literature is mixed regarding neuropsychological differences in mTBI/PTSD, and few studies have evaluated the cognitive effects of these conditions jointly. Moreover, the extent to which neuropsychological impairments affect functional outcomes in mTBI/PTSD has been understudied.

Methods: Participants in the INTRuST biorepository (N = 389) completed questionnaires assessing PTSD, depression, functional outcomes (disability, physical/mental health-related quality of life; QOL), and a neuropsychological battery assessing learning and memory, attention, processing speed, and executive functioning. Performance was compared between participants with mTBI, PTSD, both, and control participants, and associations between performance and psychiatric and functional outcomes was examined.

Results: Although groups did not differ on neuropsychological performance across most domains, the PTSD group (M = .23 (1.27)) performed significantly worse than controls (M = 1.12 (1.10)) on verbal learning and memory (MDiff = .90, SE = .25, 95% CI [.26, 1.54]). Greater psychiatric symptoms, particularly cognitive postconcussive symptoms in those with mTBI (r = .21), were associated with worse learning and memory. Worse verbal learning and memory, visuospatial memory, and attention were associated with poorer physical-mental health QOL and greater self-rated disability (rs = .17-.20).

Conclusions: Groups showed modest differences in neuropsychological profiles with most participants demonstrating intact performance, but PTSD was associated with worse verbal memory performance. Neuropsychological measures of memory and attention were associated with functional outcomes. Thus, these neuropsychological domain discrepancies may be important for understanding real-world health-related outcomes in PTSD.

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Keywords: TBI, PTSD, Quality Of Life, Neuropsychology

748. A Subject-Specific Diffusion Tensor Imaging Study of Mild Traumatic Brain Injury With and Without Post-traumatic Stress Disorder

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Background: Posttraumatic stress disorder is often comorbid with mild traumatic brain injury (mTBI). The differential diagnosis of these conditions is complicated due, in part, to their shared symptomatology. Furthermore, conventional neuroimaging contributes little to diagnosis because mTBIs are difficult to observe and heterogeneous, despite commonly resulting in diffuse axonal injury. Diffusion tensor imaging (DTI) is sensitive to diffuse axonal injuries and, thus, is more likely to detect mTBIs, particularly when analyses account for the inter-individual variability of these injuries.

Methods: With a subject-specific approach, we compared fractional anisotropy (FA) abnormalities between groups with a history of mTBI (n = 35), comorbid mTBI and PTSD (mTBI+PTSD; n = 22), and healthy controls (n = 37). We compared all three groups on the number of abnormal FA clusters derived from subject-specific profiles of injury (i.e., individual z-score maps) along the white matter skeleton.

Results: The mTBI+PTSD group evinced a greater number of abnormally low FA clusters relative to both the healthy controls and the mTBI group without PTSD (p < .05). Across the groups with a history of mTBI, increased numbers of abnormally low FA clusters were significantly associated with heightened PTSD symptom severity, depression, post-concussion symptoms, and reduced information processing speed (p < .05).

Conclusions: Our findings underscore the importance of subject-specific microstructural analyses when searching for mTBI-related brain abnormalities, especially in patients with PTSD. Our study also suggests that patients with a history of mTBI and comorbid PTSD, relative to those without PTSD, are at increased risk of FA abnormalities.

Supported By: DOF
Keywords: Mild Traumatic Brain Injury, PTSD - Posttraumatic Stress Disorder, Diffusion Tensor Imaging (DTI), Magnetic resonance imaging

749. Neurosteroids and Inflammatory Markers in PTSD and TBI

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Background: Neurosteroids are endogenous molecules synthesized de novo in brain, inadrenals, and other tissues. They demonstrate pleiotropic actions that are highly relevant to the neurobiology of PTSD and TBI. Allopregnanolone (ALLO) is a GABAergic neurosteroid with anti-inflammatory, neuroprotective, and neurogenesis-enhancing properties. We thus investigated neurosteroids and inflammatory markers in the INjury and TRaumatic STress (INTRuST) Biorepository cohort.

Methods: Serum samples were collected from seven INTRuST Biorepository sites. Neurosteroids were quantified using mass spectrometry-based methods. Inflammatory markers (cytokines, c-reactive protein [CRP]) were quantified using commercially available kits. Wilcoxon comparisons and Box-Cox regression analyses controlling for age and smoking as predetermined covariates were conducted.

Results: Allopregnanolone, pregnenolone, and androsterone levels were significantly decreased in male patients with PTSD, with or without a history of TBI (n=107) compared to male control participants (n=103); p<0.001, p=0.041, p=0.008, respectively. Reductions in ALLO (p=0.0007) and androsterone (p=0.056) persisted in the PTSD group when age and smoking were added as covariates. In male participants with a history of TBI (with or without PTSD; n=129), ALLO was similarly reduced compared to male control participants (n=103) in both Wilcoxon (p<0.001) and regression (p=0.0001) analyses. ALLO was inversely correlated with PTSD symptoms (as assessed by the PCL; p=0.0094) and depression symptoms (as assessed by the PHQ-9; p=0.0016). IL-6, IL-8, TNF-α, and CRP were significantly increased in both the PTSD and TBI groups compared to controls.

Conclusions: Neurosteroids, cytokines, and CRP are promising biomarker candidates for PTSD and TBI. These findings have potential for translation into mechanistically anchored therapeutics.

Supported By: INTRuST; VA Mid-Atlantic MIRECC

Keywords: PTSD, TBI, Neurosteroid, Inflammatory Markers, Allopregnanolone

750. Resting State Differences in PTSD and TBI in the Intrust Sample

Alan Simmons1, Jessica Bomyea2, Murray Stein3, and INTRuST Clinical Consortium41UCSD, 2VA San Diego Healthcare System, University of California, San Diego, 3Department of Psychiatry and Department of Family Medicine & Public Health, University of California, 4INTRuST

Background: In combat soldiers are at high risk for PTSD and TBI. These conditions can affect brain networks and can have deleterious effects on numerous areas of cognitive processing. There is a need for larger studies of the functional impact of these conditions. Resting state analysis has proved to be a useful tool for deriving an understanding of functioning across numerous disorders without task based biasing.

Methods: A sample of 340 subjects was collected including controls (n=160), the remaining sample (n=180) has either TBI with PTSD (n=72) or without (n=108). All subjects had resting state data that was analyzed through ICA to determine group differences. Specifically, a 2 step approach was taken in which PTSD was contrasted with matched controls and then TBI was observed and contrasted with in these networks.

Results: Network maps relating to default mode and saliency processing differed between the PTSD and Controls in a number of regions including the ACC and prefrontal cortex. Activation in saliency circuits was better explained by PTSD.

Conclusions: These findings provide further quantitative evidence of the disrupted neural networks in PTSD and TBI. The overlapping but divergent relationship between PTSD and TBI may suggest that the current categorical nomenclature can be improved upon by either a realignment or alternative (e.g., symptom focused) approach.

Supported By: INTRuST

Keywords: PTSD, mTBI, Resting state fMRI, military combat soldiers

SYMPOSIUM The Impact of Early Adversity on Molecular and Brain Biomarkers in Depression: From One Generation to the Next Saturday, May 20, 2017 - 3:00 PM - 5:00 PM Sapphire IJ Chair: Sidney Kennedy

751. The Role of Childhood Maltreatment in Depression: Overview of the Literature and Insights from the CAN-BIND Program

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1Queen’s University, 2University of Calgary, 3University Health Network

Background: Childhood maltreatment is associated with a 5-fold increase in risk for major depressive disorder. Further, adults with a history of maltreatment suffer a more severe and
chronic course, and are less likely to respond to standard antidepressants, than those without. The purpose of this talk is to provide a general overview of the literature on maltreatment and depression, and to present results pertaining to the relation of maltreatment to the endophenotype of stress reactivity in the PAD study and to treatment response in the CAN-BIND study.

**Methods:** In PAD, 41 patients and 30 healthy controls participated in a laboratory stressor and salivary cortisol was collected at 5 time points. In CAN-BIND 1 patients received 8 weeks of escitalopram treatment. Across studies, childhood maltreatment was assessed with a contextual interview and independent rating system.

**Results:** In PAD, relative to controls, childhood maltreatment in the depressed group was related to hypercortisolemia in those with mild/moderate symptoms, $F(1, 63) = 13.06, p<0.005$, and hypocortisolemia in those with severe symptoms, $F(1, 63) = 5.57, p<0.05$. In the first CAN-BIND cohort of 85 patients, emotional abuse ($R^2 = 0.08, p<0.05$) and neglect ($R^2 = 0.10, p<0.01$) were more strongly associated with baseline MADRS scores than physical or sexual abuse ($p>0.10$). However, the strongest predictor of week 8 response was sexual abuse ($R^2 = 0.05, p<0.05$).

**Conclusions:** We discuss these results in terms of their implications for the CAN-BIND goal of using enviromarkers and biomarkers to inform personalized treatment for depression.

**Supported By:** Ontario Brain Institute; Ontario Mental Health Foundation; Canadian Institutes of Health Research; Lundbeck; Servier; Bristol-Myers Squibb; Pfizer

**Keywords:** Depression, childhood maltreatment, Stress Reactivity, antidepressant response

**752. A Developmental Model of Atypical Depression Based on Dopamine and Serotonin System Gene Interaction with Pre- And Post-Natal Adversity**

Robert Levitan\(^1\), Ashley Wazana\(^2\), Cathryn Gordon-Green\(^2\), Barbara Wendland\(^3\), Patricia Silveira\(^4\), Helene Gaudreau\(^5\), Laurette Dube\(^6\), Meir Steiner\(^6\), James Kennedy\(^1\), and Michael Meaney\(^7\)

\(^1\)CAMH, University of Toronto, \(^2\)McGill University, \(^3\)University of Toronto, \(^4\)Douglas Hospital and McGill University, \(^5\)Douglas Hospital, \(^6\)McMaster University, \(^7\)Douglas Hospital, McGill University

**Background:** To develop an early developmental model of atypical depression as defined by the combination of negative affect and overeating/obesity. Prior research has demonstrated that this form of depression has both an early onset and a strong link with adversity.

**Methods:** This talk will review various findings from the Maternal Adversity, Vulnerability and Neurodevelopment project (MAVAN) demonstrating several novel ways that genes interact with the environment to establish risk for depression with overeating/obesity. MAVAN is a longitudinal Canadian cohort study of developing children starting from birth (n=550).

**Results:** Results to date have demonstrated that a multilocus score based on the dopamine-4 receptor gene (DRD4) and serotonin transporter gene 5-HTTLPR interacts with prenatal maternal depression to predict negative emotionality in the children at 36 months of age, and follows a differential susceptibility model. A separate line of study has shown that the hypo-functional seven repeat allele of DRD4 interacts with low maternal sensitivity to predict overweight and obesity in girls. The current presentation will show new data to assess whether these same interactions establish risk for the combination of negative emotionality and overeating/obesity in individual children, a phenotype consistent with atypical depression.

**Conclusions:** Recent findings from MAVAN suggest that there may be unique developmental pathways based on early G X E interactions that promote vulnerability to atypical forms of depression. If so, novel preventative strategies implemented very early in life might offer unique benefits for this common, chronic and difficult-to-treat condition.

**Supported By:** Canadian Institutes of Health Research

**Keywords:** Depression, Obesity, environmental adversity, Gene x Environment

**753. The Influence of Early Life Trauma on Epigenetic Markers in a CAN-BIND Sample of Responders and Non-Responders to Escitalopram**

Laura Fiori\(^1\), Chelsey Ju\(^1\), Jane Foster\(^2\), Susan Rotzinger\(^2\), Kate Harkness\(^3\), Sidney Kennedy\(^2\), and Gustavo Turecki\(^1\)

\(^1\)McGill University, \(^2\)University Health Network, \(^3\)Queen's University

**Background:** The experience of childhood trauma can influence the development of major depressive disorder (MDD), which results from an intricate interaction among clinical, social, genetic, and environmental factors. Furthermore, the effects of childhood adversity may extend beyond risk, and act to influence response to therapy, including antidepressant treatment.

**Methods:** Our cohort consisted of 314 subjects from the CAN-BIND study: 210 patients with MDD treated with escitalopram, and 104 healthy controls. Blood was collected at baseline and after 8 weeks for transcriptomic analyses (Illumina HT-12 microarrays and small RNA sequencing). DNA methylation was assessed at baseline (Infinium MethylationEPIC beadchip). Patients were classified as responders (>50% reduction in Montgomery-Asberg Depression Rating Scale scores) or non-responders (<50%). Childhood adversity was assessed using the Childhood Experience of Care and Abuse questionnaire.

**Results:** Of the 314 subjects, 257 completed all measures at Week 8. Approximately 50% of MDD patients responded to treatment. All samples and internal controls on the DNA methylation arrays passed quality control. We obtained high quality gene expression microarray data at both baseline and after 8 weeks of treatment. Small RNA-seq generated approximately 18M reads per subject, with an average of 511 unique microRNA and 285 with a count of over 10. An integrated analysis will be presented examining the influence of childhood experiences on gene expression and DNA methylation.
adversity and baseline DNA methylation on treatment response at week 8.

**Conclusions:** Understanding the influence of early life trauma on treatment response and identifying the associated epigenetic markers can help guide treatment selection and improve outcomes in MDD.

**Supported By:** Ontario Brain Institute; Canadian Institutes of Health Research; Lundbeck; Servier; Bristol-Myers Squibb; Pfizer

**Keywords:** Epigenetic, Early life adversity, gene expression profiling, Antidepressant response, Major Depressive Disorder (MDD)

754. Inflammatory Markers as Mediators of the Association between Early Life Adversity and Hippocampal Volume in Adult Patients with Depression: Findings from Phase 1 of the CAN-BIND Study

**Stefanie Hassel**, 1 Andrew Davis 2, Geoffrey Hall 2, Jane Foster 3, Kate Harkness 4, Jacqueline Harris 5, Mojdeh Zamyadi 6, Stephen Arnott 6, Gesine Alders 2, Susan Rotzinger 3, Stephen Strother 6, Sidney Kennedy 3, and Glenda MacQueen 5

1Aston University, 2McMaster University, 3University Health Network, 4Queen’s University, 5University of Calgary, 6Rotman Research Institute, University of Toronto

**Background:** Hippocampal volume changes and elevated prevalence of early childhood adversity (ECA) are frequently reported in major depressive disorder (MDD). Whether hippocampal volume reduction poses an increased risk for depression or is a consequence of ECA remains unclear, although evidence for childhood trauma exacerbating changes in hippocampal volume exists. Alterations in the inflammatory system of MDD patients may play a role in mediating adverse effects of early life stress in these patients. Here, we use integrated neuroimaging, clinical and molecular data from the first phase of CAN-BIND.

**Methods:** Clinical data, measures of childhood adversity (assessed by the Childhood Experience of Care and Abuse (CECA)) and structural neuroimaging data were collected for 80 MDD patients (49 females), and 59 age- and gender-matched healthy controls (HC; 40 females), across six study sites in Canada. Four different 3T magnetic resonance imaging systems were used to acquire whole-brain T1-weighted images using a gradient echo sequence. Freesurfer, an automated segmentation software, was used to segment hippocampal and total intracranial volume (ICV); a standardized protocol as developed by ENIGMA (http://enigma.ini.usc.edu/protocols/imaging-protocols/) was used for quality control of segmented structures.

**Results:** Patients with MDD reported early childhood adversity significantly more often than HC (X2(2,n=139)=14.8, p<0.001) and MDD with ECA had decreased left (t(74)=2.9, p<0.005) and total (t(74)=2.3, p<0.05) hippocampal volume relative to MDD without ECA. MDD patients and HC did not differ in hippocampal volume.

**Conclusions:** The complex association between ECA, changes in hippocampal volume and the role of inflammatory markers in relation to depression will be discussed.

**Supported By:** Canadian Institutes of Health Research; Ontario Brain Institute; Lundbeck; Servier; Bristol-Myers Squibb; Pfizer

**Keywords:** Depression, Hippocampal Volume, Early Life Stress, Neuroimaging, Inflammatory Markers

755. The Enigma Bipolar Disorder Working Group: Recent Structural and DTI Findings from the Largest Neuroimaging Study of Bipolar Disorder (N=6,500)

**Ole Andreassen**, 1 Christopher Ching 2, Paul M. Thompson 3, and ENIGMA Bipolar Disorder Working Group 4

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**Background:** Previous MRI studies of bipolar disorder (BD) are often limited by small sample sizes and heterogeneity exists with regard to neuroimaging markers. To address these limitations, the ENIGMA Bipolar Disorder Working Group collected the largest BD neuroimaging data set ever studied (N=6,500). Utilizing the ENIGMA processing and analysis protocols allows for unprecedented power to detect BD-related brain variation in this large, worldwide cohort. Here, we present recent findings from both diffusion weighted imaging and subcortical shape analysis.

**Methods:** ENIGMA harmonized analysis methods were applied to 28 international pooled study samples of MRI data and involved subcortical shape and diffusion weighted imaging analyses. We assessed differences between BD and healthy controls (CN) using both mega- and meta-analytic multiple linear regression models, adjusting for standard covariates (age, sex, etc.), and correcting for multiple comparisons using a standard FDR correction.

**Results:** Subcortical shape analysis revealed patterns of both increased and decreased local thickness in BD compared to CN across a number of subcortical structures. Initial analyses of diffusion MRI data indicate widespread fractional anisotropy (FA) reductions in BD patients compared to CN.

**Conclusions:** Subcortical shape analysis provides the ability to map subtle variations in local subcortical shape morphometry and may reveal the pattern of BD-related
burden across these subcortical structures. Reductions in FA display a pattern of widespread white matter alteration beyond the fronto-limbic disruption described in the current models of BD. The ENIGMA pipeline will allow for comparisons of brain measures across disease groups in what will be the largest cross disorder analysis ever conducted.

Supported By: NIH grant U54 EB040203, EU, RCN, KGJ
Keywords: Bipolar Disorder, Neuroimaging, subcortical volumes, subcortical shape, Mood Stabilizers

756. The Enigma 22q11.2 Deletion Working Group: Insights into Neurodevelopment and Psychosis
Christopher Ching1, Julio Villalon Reina2, Daqiang Sun3, Carrie Bearden1, and ENIGMA 22q11.2 Deletion Working Group

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Background: 22q11.2 deletion syndrome (22q-Del) is a recurrent copy number variant that is among the greatest known genetic risks for psychosis (30-fold increase); It is also highly penetrant for developmental neuropsychiatric conditions. Here, the ENIGMA 22q11.2 Working Group reports the largest-ever neuroimaging study of cortical, subcortical, and diffusion imaging differences between 22q-Del and healthy controls (CN).

Methods: We applied ENIGMA harmonized methods to brain MRI data from 9 scan sites (22q-Del=408; CN=349) to analyze cortical morphometry, subcortical shape and volumes, and diffusion-weighted imaging measures. We assessed group differences using multiple linear regression methods, and investigated convergent patterns of abnormal morphometry in 22q-Del and idiopathic schizophrenia by comparing our data with the ENIGMA Schizophrenia Working Group (N~8000).

Results: Analyses revealed widespread cortical surface area reductions in 22q-Del compared to CN, with opposite effects for cortical thickness. Regions of surface area reduction in 22q-Del with psychosis showed significant overlap with those regions most affected in schizophrenia, particularly involving the superior temporal gyrus, cingulate, and sensorimotor/regions. Novel subcortical shape models revealed complex patterns of localized reduction and enlargement for 22q-Del versus CN across all 7 bilateral subcortical structures. Finally, analysis of DTI measures revealed brain regions with higher and lower FA in 22q-Del participants versus controls.

Conclusions: The ENIGMA 22q11.2 Working Group assessed the largest-ever sample of 22q11-related brain data. Complex and widespread morphometric and DTI alterations generally agree with prior smaller studies of 22q-Del. In partnership with the ENIGMA Schizophrenia group, our harmonized methods suggest complex neurobiological relationships between 22q-Del and schizophrenia.

Supported By: NIH grant U54 EB040203; NIMH Grant RO1 MH085953
Keywords: Brain Imaging, Shape Analysis, Diffusion Tensor Imaging (DTI), Multimodal neuroimaging, 22q11 Deletion Syndrome

757. Machine Learning Insights from Enigma's Studies of Major Depressive Disorder: Classification via Distributed Analysis
Daijiang Zhu1, Paul M. Thompson2, Lianne Schmaal3, Dick Veltman4, and ENIGMA Major Depressive Disorder Working Group

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Background: Major depressive disorder (MDD) affects over 350 million people worldwide. Unfortunately, early diagnosis of MDD remains challenging and is based on behavioral criteria. Here we provide a multi-site machine learning method to select structural neuroimaging features that best predict major depression diagnosis.

Methods: Brain MRI data from 8 cohorts within the ENIGMA MDD Working Group (over 1,800 participants) were processed using harmonized ENIGMA protocols to derive several measures of brain morphometry including subcortical volume, and cortical thickness and surface area. We applied our newly developed “Distributed LASSO” machine learning method to discover imaging predictors that discriminate MDD patients from healthy controls, taking into account information distributed across multiple centers. The method works by combining predictive neuroimaging features using multi-layer perceptron classification, does not require the sharing of individual-level data, and uses the combined computational infrastructure and information at several international centers to make and verify discoveries.

Results: Features identified by the distributed Lasso technique were all cortical thickness measures – consistent with our prior study indicating significant univariate cortical thickness differences between adult MDD and HC. Overall, our distributed Lasso technique increased accuracy, specificity, and sensitivity of MDD classification over simply using all predictors without feature selection.

Conclusions: This analysis represents the largest study of MDD classification to date. Future work aims to include DTI, fMRI, and genomic data to see which metrics improve classification. Taking advantage of a large, multi-site cohort, this distributed computing framework may assist large-scale collaborative discovery of factors that improve the classification of mental illness and prognosis.

Supported By: NIH grant U54 EB040203
Keywords: Major Depression, Brain Imaging, Machine learning, Classification algorithms
758. Harmonized Large-Scale Anatomical Shape Analysis: Mapping Subcortical Differences across the Enigma Bipolar, Schizophrenia, and Major Depression Working Groups

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Background: Subcortical volumes are known to be affected across the family of affective disorders, such as Bipolar Disorder (BD), Schizophrenia (SCZ) and Major Depressive Disorder (MDD). However, volume alone remains a crude morphometric measure, sometimes failing to identify subtle disorder-specific effects. The ENIGMA Shape Analysis Pipeline aims to explore more complex morphometric measures such as vertex-wise shape features of subcortical structures.

Methods: We apply a Medial Demons protocol to assess subcortical shape differences in seven bilateral subcortical regions: thalamus, hippocampus, amygdala, putamen, globs pallidus, nucleus accumbens and the caudate nucleus. To make comparisons across disorders, we apply a formal non-parametric test for morphometric concordance in each region, comparing effect location distributions for disorder pairs. We compared effects of 2,418 Schizophrenia patients versus 3,343 controls, 534 Bipolar patients versus 1,022 controls, and 653 MDD patients versus 983 controls. All results were FDR corrected.

Results: Significant shape effects in all 14 regions in SCZ, bilateral thalamus, hippocampus, and putamen in BD, and left pallidum and thalamus effects in MDD. No MDD effects were concordant with SCZ; however, the left thalamus (p<0.0005) and both left (p=0.006) and right (p<0.0005) putamen were concordant in their effect maps between BD and SCZ.

Conclusions: All three disorders discussed here have been associated with reduced subcortical volume. The ENIGMA Subcortical Shape Analysis Pipeline allows for mapping of subtle variations that may not be captured by analysis of gross volume. Furthermore, our technique allows us to compare patterns of disease-related vulnerability within certain subfields across disorders with unprecedented power.

Supported By: NIH grant U54 EB040203

Keywords: Major Depression, Bipolar Disorder, Schizophrenia, Shape Analysis

759. Whole Blood MicroRNA Expression Following ECT: A Role for VEGF in Psychotic Depression

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Background: MicroRNAs are small non-coding molecules that can regulate the expression of hundreds of genes. Little is known about microRNAs in ECT. We therefore studied changes in microRNA expression in patient peripheral blood after ECT as this may reflect changes in the brain.

Methods: Depressed patients were participants in the EFFECT-Dep Trial (ISRCTN23577715). A deep sequencing (SOLID™ platform) discovery-phase study of peripheral blood microRNA expression before/after ECT (n=16) was followed by qRT-PCR confirmation. Candidate microRNAs were validated in a separate cohort (n=37 patients, n=34 controls) and bioinformatic analyses identified gene targets. Downstream mRNA changes were quantified using qRT-PCR (n=97 patients, n=53 controls). Depression severity was measured with the Hamilton Depression Rating Scale, psychosis severity with the 5-item BPRS.

Results: After correction for multiple testing, we did not identify any differentially expressed microRNAs in the group as a whole. However, significant changes were seen in a subgroup with psychotic depression. These candidate microRNAs were validated in a separate cohort. In patients with psychotic depression, miR-126-3p (p=0.006) and miR-106a-5p (p=0.025) were raised at baseline compared to controls, with levels normalising post-ECT. Shared targets of miR-126-3p and miR-106a-5p include VEGFA. VEGFA mRNA was significantly increased in depressed subjects compared to controls (p=0.001). In psychotic depression only, VEGFA levels decreased significantly following ECT (p=0.010), and baseline VEGFA levels correlated with depression (r=0.302, p=0.003) and psychosis severity (r=0.505, p=0.02).

Conclusions: Significant changes in miR-126-3p, miR-106a-5p and their shared target VEGFA were seen in psychotic depression treated with ECT, indicating that molecular differences exist between psychotic and non-psychotic depression.

Supported By: NIH grant U54 EB040203
Saturday Abstracts

760. Continuation ECT for Relapse Prevention in Depressed Elderly. Results From the Pride Study

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Northwell Health System

Background: The randomized phase of the Prolonging Remission in Depressed Elderly (PRIDE) study evaluated the efficacy and tolerability of continuation ECT plus medication compared with medication alone in depressed geriatric patients after a successful course of ECT.

Methods: PRIDE was a two-phase multisite study. Phase 1 was an acute course of right unilateral ultrabrief pulse ECT, augmented with venlafaxine. Phase 2 compared two randomized treatment arms: a medication only arm (venlafaxine plus lithium, over 24 weeks) and an ECT plus medication arm (four continuation ECT treatments over 1 month, plus additional ECT as needed, using the Symptom-Titrated, Algorithm-Based Longitudinal ECT [STABLE] algorithm, while continuing venlafaxine plus lithium). The intent-to-treat sample comprised 120 remitters from phase 1. The primary efficacy outcome measure was score on the 24-item Hamilton Depression Rating Scale (HAM-D)..

Results: At 24 weeks, the ECT plus medication group had statistically significantly lower HAM-D scores than the medication only group. The difference in adjusted mean HAM-D scores at study end was 4.2 (95% CI=1.6, 8.9).

Conclusions: Additional ECT after remission (here operationalized as four continuation ECT treatments followed by further ECT only as needed) was beneficial in sustaining mood improvement and outperformed medication alone for efficacy and global cognitive function outcomes.

Supported By: NIMH UO1
Keywords: Electroconvulsive therapy, Major Depression, Relapse Prevention, Venlafaxine, Lithium

761. Continuation Electroconvulsive Therapy for Clozapine-Resistant Schizophrenia

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Background: In a previous study, we showed that Electroconvulsive therapy (ECT) can be very effective for the acute treatment of clozapine resistant schizophrenia. In this presentation we show pilot data describing efficacy of continuation - i.e. post-acute - ECT for patients that showed response to the combination of acute ECT and clozapine.

Methods: The sample was recruited from completers of a single blind RCT, in which we evaluated the efficacy of ECT for clozapine-resistant schizophrenia. Continuation ECT was offered for all responders from the acute phase. The continuation phase lasted for up to 24 weeks, during which patients received bilateral ECT, following a tapered schedule for a total of 10 treatments in 6 months.

Results: Thirteen patients agreed to participate. Their mean BPRS-PS at continuation baseline was 7.69 (+ 3.66) and at the end of the study 9.2 (+ 4.32). Six of the 13 patients (46.1%) completed the 6-month study. None of the patients had relapsed at the time they exited the study. No patient discontinued treatment because of side effects or worsening of psychotic symptoms. The combination of ECT and clozapine was well tolerated.

Conclusions: These data suggest that maintenance ECT plus clozapine can be protective against relapse for those patients with clozapine-resistant schizophrenia who responded to an acute course of ECT, at least in the first six months after the acute phase. Further research is needed to confirm the efficacy and establish the optimal duration and frequency of maintenance ECT in this population.

Supported By: NIMH
Keywords: Schizophrenia, Electroconvulsive therapy, clozapine, relapse protection

762. The Mortality Rate of Electroconvulsive Therapy: Results from a Systematic Review and Meta-Analysis

Nina Torring2, Sohag N Sanghani3, Georgios Petrides3, Charles H Kellner4, and Soren Dinesen Ostergaard1

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Background: Electroconvulsive therapy (ECT) is a highly effective treatment for a wide range of mental disorders, but remains underutilized because of fears of cognitive and medical risks, including the risk of death. In this study we aimed to assess the mortality rate of ECT by means of a systematic review and meta-analysis.

Methods: The study was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The ECT-related mortality rate was calculated as the total number of ECT-related deaths reported in the included studies divided by the total number of ECT treatments. The associated 95% Confidence interval (95%CI) was calculated using Bernoullis principle of distribution.

Results: 14 studies with data from 32 countries reporting on a total of 757,662 ECT treatments met the inclusion criteria. 15 cases of ECT-related death were reported in the included studies yielding an ECT-related mortality rate of 2.0 per
100,000 treatments (95%CI: 1.0-3.0). In the eight studies that were published after 2001 (covering 406,229 treatments), there were no reports of ECT-related deaths.

Conclusions: The ECT-related mortality rate was estimated at 2.0 per 100,000 treatments. In comparison, a recent meta-analysis on the mortality of general anaesthesia in relation to surgical procedures reported a mortality rate of 3.4 per 100,000. Our findings document that death caused by ECT is an extremely rare event. This information can be used to reassure concerned parties, including patients in need of ECT.

Supported By: The Lundbeck Foundation

Keywords: Nicotine Dependence, Resting state fMRI, Satiety vs. Withdrawal

764. Homeostatic and Hedonic Food Motivation in Adolescent Low-Weight Eating Disorders before and after a Standardized Meal

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Background: Low-weight eating disorders (LWEDs) frequently onset in adolescence and are characterized by persistent food restriction despite self-starvation. The pathophysiological mechanisms underlying restriction, particularly in adolescence proximal to symptom onset, are unknown. We hypothesized that healthy adolescent controls would show increased neural activity in homeostatic and hedonic food motivation pathways in fasting state compared to postprandial assessment, while adolescents with LWEDs would show hypoactivation in food motivation circuitry after both prolonged fast and a satiating meal.

Methods: Twenty-two females with LWEDs (M=19.35 years, SD=2.46 years) and 11 age-matched controls completed a multi-disciplinary assessment involving (1) functional magnetic resonance imaging (fMRI) while viewing food and non-food stimuli before and after a standardized meal, (2) the Eating Disorder Examination, and (3) self-report measures of appetite and reward.

Results: Compared to controls, LWEDs demonstrated premeal fMRI hypoactivation (high-calorie food > objects) in the orbitofrontal cortex, insula, hippocampus, midbrain, and dorsolateral striatum (p<.05) and marginally in the amygdala (p=.06). While in controls fMRI activation of food motivation brain regions was attenuated postmeal, LWEDs had reduced activation of this circuitry premeal without further attenuation postmeal. Premeal fMRI hypoactivation was associated with increased dietary restraint and reduced self-reported appetite and reward.

Conclusions: These are the first data demonstrating that homeostatic and hedonic food motivation pathways are hypoactive in adolescents with LWEDs, highlighting an important neurodevelopmental mechanism of illness that could be targeted in future treatment trials. Furthermore,
765. The Impact of Fasting and Eating on Control and Reward Responses in Women Remitted from Bulimia Nervosa

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**Background:** Bulimia nervosa (BN) is associated with altered activation in inhibitory control and reward circuitry. However, it is unclear whether this dysfunction is exaggerated a) when fasted, potentially increasing vulnerability to binge eating initiation, or b) after eating has started, potentially contributing to difficulty stopping eating.

**Methods:** Women remitted from BN (RBN; n = 26) and control women (CW; n = 22) performed a parametric Stop Signal Task and were administered tastes of water or a sucrose solution during fMRI on two counterbalanced visits —after a 16-hour fast or a standard meal.

**Results:** Across metabolic states, groups performed similarly on the stop task, but activation during successful hard trial inhibition depended on metabolic state. After eating, when correctly inhibiting responses, RBN women showed greater activation than CW in left DLPFC. RBN also showed greater activation in this region during inhibition when fed compared to when they were fasted. CW were significantly more responsive to taste when fasted compared to when fed in the left putamen and left amygdala. In contrast, RBN response to taste did not differ between states. Compared with CW, RBN participants showed greater activation in the left amygdala when fed.

**Conclusions:** Findings suggest potential neural mechanisms underlying fast-binge-purge cycles. Individuals with BN may require fewer prefrontal resources to inhibit responses when fasted, but greater effort to maintain the same level of control when fed. Further, food reward may not be appropriately devalued after eating. Interventions focused on the post-meal period may be most effective.

**Supported By:** R01MH086017; R01MH042984-17A1; The Price Foundation

**Keywords:** Bulimia Nervosa, Inhibitory Control, Reward, BOLD fMRI

766. Impact of Acute and Habitual Intake on Brain Processing of Food Stimuli and Functional Connectivity

Kyle Burger, Grace Shearrer, and Jennifer Gilbert

University of North Carolina at Chapel Hill

**Background:** Complications associated with obesity are a major public health problem in industrialized nations. Theories suggest obesity is related to aberrant brain response patterns during food related tasks and while at rest. Yet, little is known about the temporal precedence, i.e., cause and effect of these relations.

**Methods:** To examine the impact of acute and habitual sugar intake on brain response patterns while at rest and during beverage anticipation and intake, we completed two studies. In study 1, we measured brain connectivity in sample of healthy-weight (n = 13) and obese participants (n = 12) using resting-state fMRI scans after an overnight fast and after consumption of a high-sugar meal. In Study 2 we randomly assigned 20 healthy-weight individuals consumed of 1 of 2 flavored sugar-sweetened beverages for 21 days. Participants underwent 2 fMRI sessions to assess BOLD response to beverage stimuli and resting-state functional connectivity.

**Results:** In study 1, in addition to differences as a function of weight status and due to feeding, obese individuals showed significant decreased sensitivity to food intake in connectivity between the amygdala and dorsal anterior cingulate cortex emerged (pFDR = 0.0397). In study 2, daily beverage consumption resulted in decreases in dorsal striatal response during receipt of the consumed beverage (r = −0.46), and decreased ventromedial prefrontal response during logo-elicited anticipation of the consumed beverage (r = −0.44), but no changes in resting state functional connectivity.

**Conclusions:** Results appear to implicate weight status in differences in resting state functional connectivity, and eating behavior patterns in aberrant brain response to specific food stimuli.

**Keywords:** Obesity, fMRI, Functional connectivity, Food-craving

**SYMPOSIUM**

**Interaction of Inflammatory Signals between Body and Brain in Psychosis and Suicide**

Chair: Thomas Weickert

Saturday, May 20, 2017 - 3:00PM - 5:00PM
Aqua 300 AB

**767. Evidence for Blood-Brain Barrier Disruption and Antibody Presence in Brains of People with Schizophrenia**

Cynthia Shannon Weickert1, Helen Cai2, Lara Glass1, Maree Webster3, Danny Boerrigter1, Duncan Sinclair2, and Vibeke Catts1

1Neuroscience Research Australia, 2University of New South Wales, 3Stanley Medical Research Institute

**Background:** Elevated inflammatory cytokine mRNAs are found in 38% of people with schizophrenia. This high inflammation schizophrenia group has increased astroglia, implicating blood-brain barrier (BBB) alterations. Cytokines and antibodies crossing the BBB enter the brain and may contribute to neuropathology. Peripheral brain reactive
immunoglobulin-γ (IgG) is reported in people with schizophrenia-like symptoms and monoclonal antibodies blocking cytokines are used in clinical trials. It is not known if IgG is present in human cortex or if brain IgG levels differ between schizophrenia and controls.

Methods: Eight transcripts related to BBB function were measured by qPCR in dorsolateral prefrontal cortex (DLPFC) in 37 people with schizophrenia/schizoaffective disorder and 37 controls. Immunohistochemistry localized intercellular adhesion molecule-1 (ICAM-1) and brain IgGs. Western Blotting quantified IgGs. We predicted more BBB transcripts and brain IgGs in high inflammation schizophrenia versus low inflammation schizophrenia and control groups.

Results: Toxin efflux transporter (ABCG2) mRNA was lower and ICAM-1 mRNA was higher in schizophrenia versus controls. The high inflammation schizophrenia group had significantly lower ABCG2 and higher ICAM-1 mRNAs versus low inflammation groups. Blood vessel endothelium luminal walls and astrocytes contained ICAM-1. IgGs surrounded DLPFC blood vessels in schizophrenia and controls. IgG proteins did not differ between diagnostic groups; however, there was a trend for decreased brain IgG in high inflammation schizophrenia (p=0.06).

Conclusions: Brain inflammation may alter BBB function to attract more white blood cells via increased ICAM-1 which may contribute to schizophrenia neuropathology. IgG in brain parenchyma suggests that damaging and protective antibodies could access brain in health and disease.

Supported By: Stanley Medical Research Institute, NSW Health, Macquarie Group, NHMRC Australia

Keywords: Schizophrenia, Cytokine, Autoantibodies, Dorsolateral Prefrontal Cortex, Blood brain barrier

768. Intestinal Inflammation and Suicidal Behavior

Faith Dickerson1, Holly Wilcox2, and Robert Yolken2

1Sheppard Pratt Hospital, 2Johns Hopkins School of Medicine

Background: Intestinal inflammation is associated with psychiatric disorders but has not been studied as to the association with suicide behavior.

Methods: The Columbia Suicide Severity Rating Scale was administered to 164 psychiatric patients (62 schizophrenia, 65 bipolar disorder, and 37 major Depression). The mean age was 37.7 years (± 13.5); 54% were male and 53% were inpatients. Data from 292 non-psychiatric controls were also analyzed. Psychiatric participants were classified into one of three groups: suicide attempt in the past month; lifetime suicide attempt but not past month, and no suicide attempt history. Blood samples were collected to measure markers of intestinal inflammation including antibodies to gliadin and Saccharomyces cerevisiae. We also measured C-reactive protein, and antibodies to the protozoan Toxoplasma gondii. Linear regression analyses were employed to analyze the association between immune markers and suicide attempt history adjusting for demographic variables.

Results: A total of 18 (11%) individuals had a suicide attempt in the past month; 73 (46%) in the lifetime but not past month. A suicide attempt in the past month was associated with elevated levels of IgA class antibodies to ASCA (t=3.08, p=.002) and IgG antibodies to gliadin (t=2.45, p=.014). Having a lifetime history of a suicide attempt was associated with elevations in CRP (t=2.91, p=.004).

Conclusions: Measures of inflammation are linked to suicide behaviors. An increased understanding of these associations might result in improved prediction of suicidal behaviors and novel preventative interventions.

Supported By: Stanley Medical Research Institute (07R-1690)

Keywords: suicide, Inflammation, Immune System

769. Immune Pathways Associated with Diet, Psychiatric Disorders, and Suicide Attempts

Robert Yolken1 and Faith Dickerson2

1Johns Hopkins University, 2Sheppard Pratt Hospital

Background: Bipolar Disorder is characterized by episodes of mania and depression and a high rate of suicide. Previous studies have indicated that many individuals with bipolar disorder have altered levels of immune activation and gastrointestinal permeability.

Methods: We analyzed dietary exposures in a population of individuals with psychiatric disorders and controls. We also examined the effect of exposures in a rat model of feeding and behavior.

Results: We found a strong association between having an episode of acute mania eating cured meat products, largely in the form of beef or turkey jerky (Odds ratio 3.75, 95% CI 2.3–6.0 p<0.002 adjusted for age, gender, and race) There was also a strong association between eating cured meat and a history of suicide attempts (Odds ratio 6.4, 95% CI 1.7–23.2, p<0.002). We developed a rat model examining the effects of cured meat on behavior and brain functioning. We found that the feeding of nitrate containing cured meat resulted in altered behavior and cognition. This feeding was associated with the activation of the mTOR pathway in the hippocampus as evidenced both by altered gene expression and changes in the phosphorylation of target proteins. The consumption of control preparations not containing increased levels of nitrates did not alter these activities. We also found that individuals with mania and other psychiatric disorders have marked alterations in components of the mTOR pathway.

Conclusions: Further elucidation of the effects of nitrated foods and the mTOR pathway may lead to new methods for the prevention and treatment of psychiatric disorders

Supported By: Stanley Medical Research Institute

Keywords: Immunomodulation, Immune System, Metabolism, diet

770. C-Reactive Protein as a Marker of Inflammation in Acute Psychosis and Schizophrenia

Thomas Weickert1, Isabella Jacomb2, Clive Stanton3, Rhini Vasudevan3, Hugh Powell3, Dennis Liu4,
Cherrie Galletly¹, Rhoshel Lenroot¹, Maryanne O’Donnell³, and Cynthia Shannon Weickert²

¹University of New South Wales, ²Neuroscience Research Australia, ³Prince of Wales Hospital, ⁴Northern Adelaide Local Health Network, ⁵University of Adelaide

Background: There is increasing evidence for the role of the inflammation in schizophrenia. Immune alterations have been shown in subgroups of patients with schizophrenia. C-reactive protein (CRP) is an acute phase reactant protein mainly produced by hepatocytes in response to an increase in circulating pro-inflammatory cytokines. Recent meta-analyses have reported a high prevalence of elevated CRP in schizophrenia which has been associated with acute psychosis and impaired cognition in schizophrenia.

Methods: Here, we examine the prevalence of CRP as a marker of inflammation in two independent samples of individuals with psychosis: 1) individuals with acute psychosis and 2) chronically ill people with a diagnosis of schizophrenia. Elevated CRP levels were defined as ≥ 3mg/L.

Results: In the acutely ill sample, significantly more patients had elevated CRP levels (60% having a CRP level above normal). Patients with acute psychosis also displayed significantly increased neutrophil-to-lymphocyte ratio (NLR) levels and a significantly higher proportion (67%) had positive anti-nuclear antibodies. In acutely ill patients with psychosis CRP and NLR levels remained consistently high at repeated admissions. In the chronically ill patients with schizophrenia, CRP levels were significantly elevated compared to healthy controls, with 44% of chronically ill patients displaying clinically elevated CRP levels. The elevated CRP group of chronically ill patients displayed significantly worse working memory ability.

Conclusions: Taken together, the present findings support previous findings suggesting that inflammatory markers decrease with resolution of acute psychotic symptoms and further support the use of adjunctive anti-inflammatory treatments in schizophrenia.

Supported By: NHMRC

Keywords: Schizophrenia, psychosis phenotype, C-reactive protein

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SYMPOSIUM
Understanding and Arresting Neuroprogression in Bipolar Disorder
Saturday, May 20, 2017 - 3:00 PM - 5:00 PM
Aqua AB
Chair: Angelos Halaris

772. The Role of the Microbiome in Bipolar Disorder-A New Model

Robert Yolken¹ and Faith Dickerson²

¹Johns Hopkins University, ²Sheppard Pratt Hospital

Background: Numerous studies indicate that immune activation occurs in individuals with bipolar disorder and other psychiatric disorders and is responsible for neuroprogression in many cases. However the source of the immune activation is largely unknown. One potential source of immune modulation and neuroprogression is the population of microorganisms which inhabit mucosal surfaces such as the gastrointestinal tract, nasopharynx, skin, and urinary tract. These organisms, collectively known at the microbiome, are acquired in early life but can be modulated by dietary and other exposures. In addition, the composition of the microbiome is partly under genetic control rendering it a
source of gene-environmental interactions. Studies in animal models indicate that the microbiome plays a central role in cognition and behavior and may be involved with neuroprogression through pathways involving innate immunity. Methods: We employed metagenomic sequencing and immunoassays to characterize the microbiome and immune activation in individuals with schizophrenia, bipolar disorder, major depression, and controls. Regression models were employed to compare groups controlling for demographic and clinical covariates. Results: We found that the microbiome is altered in many individuals with schizophrenia and mood disorders. Alterations in the microbiome are associated with an increased rate of gastrointestinal symptoms and autoimmunity in disorders in these populations. We also found that environmental factors which perturb the microbiome, such as antibiotics and dietary exposures are associated with an increased rate of mood disorders. Conclusions: The control of the microbiome may lead to totally novel methods for the prevention and treatment of the neuro-progression of human psychiatric disorders.

Supported By: Stanley Medical Research Institute

Keywords: autoimmunity, Immune System, Inflammation, infection

773. Neuroimaging Abnormalities Identify Neuroprogressive Course of Bipolar Disorder

Jair Soares

The University of Texas Medical School at Houston

Background: Evidence suggests that bipolar disorder (BD) patients who have been ill longer and have a higher number of episodes may develop more pronounced abnormalities in fronto-limbic brain regions and interconnected circuits. A current hypothesis proposes that such brain changes may be mediated by inflammatory mechanisms - possibly as a result of sustained stress.

Methods: We have utilized high resolution 3D T1 weighted MRIs, as well as diffusion tensor imaging (DTI) to examine the brains of bipolar patients and matched healthy controls, as well as neurocognitive testing utilizing the CANTAB battery. These were a collection of studies conducted by our lab over the past 15 years, across 3 different sites: San Antonio, Chapel Hill and Houston.

Results: Publications from these studies and globally point to fronto-limbic brain abnormalities in children and adolescents, as well as adults with BD. Such abnormalities include disruption in fiber pathways interconnecting fronto-limbic regions of the brain, as well as subtle anatomical changes identified with structural MRI. These changes are generally correlated with length of illness, number of illness episodes and other indicators of more severe illness subtype. We will review findings of our ongoing studies and share most recent results.

Conclusions: Fronto-limbic brain abnormalities in BD patients are well documented. There is growing evidence to suggest that such changes are progressive and worsened by repeating illness episodes. A compelling hypothesis that remains to be tested in future studies with appropriate in vivo imaging techniques is that neuroinflammation may mediate such brain changes.

774. Modulation of Immune System Activation May Arrest Neuroprogression in Bipolar Disorder

Angelos Halaris

Loyola University Medical Center

Background: Incomplete or unsatisfactory treatment responses in BD, especially the depressed phase, are well established. Immune system dysregulation in BD has been described. We hypothesized that modulation of the inflammatory response in BD by co-administration of the COX-2 inhibitor, celecoxib, would reverse treatment resistance, augment overall response and show a faster onset of antidepressant drug action.

Methods: This was a randomized, double-blind, two-arm, placebo-controlled study preceded by a screening visit, a 1-week washout and a 1-week placebo run in. If subjects continued to score 18 on the HAMD-17 scale, they were randomized to receive ESC + CBX, or ESC + PBO. They were treated for 8 weeks. Assessments were performed at weeks 1, 2, 4 and 8. Biomarkers of inflammation were obtained at specified time points and were correlated with symptom severity and treatment outcome. A total of 65 subjects were randomized and 55 subjects completed the study.

Results: Modulation of the inflammatory response reversed TRD and produced a statistically significantly better antidepressant response and a statistically significant week-1 antidepressant response in subjects on ESC + CBX only. Remissions were significantly higher on the combination. Anxiety scores also showed a significantly greater improvement with combined treatment. Specific inflammation biomarkers (hsCRP and IL1β) correlated with treatment response in the ESC + CBX group only.

Conclusions: Addition of a COX-2 inhibitor reverses treatment resistance in BD while achieving an augmented and accelerated antidepressant response. Modulation of inflammation in depression is of major clinical significance and scientific interest in biological psychiatry and clinical neuroscience.

Supported By: Stanley Medical Research Institute

Keywords: Bipolar Disorder, Treatment Resistant Depression, inflammation, COX-2 inhibition, Biomarkers

SYMPOSIUM

Discovery and Evaluation of Neural Translational Measures for Improving Therapeutic Discovery for Mental Disorders

Saturday, May 20, 2017 - 3:00 PM - 5:00 PM
Aqua C
Chair: Jared Young
775. Aberrant Error Processing in Depressive Phenotypes: Cross-species Confluence and Initial Electrophysiological Markers

Diego Pizzagalli1, Alexis Whitton1, Ashlee Van’t Veer2, Rachel Donahue1, and William Carlezon1

1Harvard Medical School/McLean Hospital, 2NIH

Background: Depression is characterized by deficits in cognitive control, including impaired performance after errors. Particularly, event-related potential (ERP) studies have shown that these impairments are linked to potentiated responses in paralimbic regions, coupled with reduced recruitment of cognitive control regions (dorsolateral prefrontal cortex). Despite these advances, several gaps remain. First, it is unclear whether such disruptions persist after remission. Second, little is known about whether similar post-error deficits emerge in rodent models relevant to depression.

Methods: 128-channel ERPs were recorded while 30 unmedicated individuals with remitted depression (rMDD) and 34 healthy controls performed an Eriksen Flanker task before and after an acute psychosocial stressor. In rats, post-error behavioral adjustments were evaluated during a 5-choice serial reaction time task after treatment with corticotropin-releasing factor (CRF), a peptide capable of inducing depression-like phenotypes in rodents. In a second rat cohort, we tested whether abnormal post-error adjustments could be reversed by treatment with JDTic, a kappa-opioid receptor antagonist that produces antidepressant-like effects.

Results: In humans, the acute stressor reduced frontocingulate activation for the rMDD – but not control – group, in regions critically implicated in cognitive control. Stress-induced blunting in frontocingulate activation was associated with dysregulated endocrinological (cortisol) and affective responses to the stressor. In rats, CRF significantly degraded post-error accuracy, but this effect was reduced by JDTic.

Conclusions: ERP markers indicate that cognitive control deficits persist after remission, pointing to a potential mechanism for increased relapse risk. Highlighting translational potential, abnormal post-error behavioral adjustments could be recapitulated in a rodent model (CRF administration) relevant to depression.

Supported By: NIMH R01MH68376 (to DAP), NIMH R01MH063266 (to WAC)

Keywords: Depression, Neuroimaging, Psychosocial Stress, Cortisol, Translational research

776. Simultaneous Intra- And Extracranial Recording of Prefrontal Neural Activity in Awake, Behaving Rats

Andre Der-Avakian1, Jesper Vernooij2, Samuel Barnes2, Eran Mukamel2, and Stefan Leutgeb2

1Department of Psychiatry, UCSD School of Medicine, 2UC San Diego

Background: In order to improve translation between human and rodent assessments of cognitive behavior, we developed a rat version of a human probabilistic reward learning task. While there is similarity in task performance between both species, it is unclear whether these behaviors are supported by corresponding neural circuits and would thus elicit related neurophysiological signals across species. Furthermore, studies in rodents typically assess neurophysiological markers of cognitive behavior using intracranial recording techniques (e.g., local field potentials; LFP), while most studies in humans are limited to extracranial techniques (e.g., electroencephalogram, EEG). To address these limitations, we developed a novel procedure to simultaneously record medial prefrontal cortical LFP and EEG activity in awake, behaving rats.

Methods: Wistar rats were surgically implanted with a 16-channel probe in the medial prefrontal cortex of one hemisphere, spanning the cingulate and prelimbic cortices, and with epidural screws over the contralateral frontal area, retrosplenial cortex, and visual cortex. After recovery, EEG and LFP signals were recorded.

Results: Prefrontal frequency bands measured using LFP were similar to prefrontal frequency bands measured using EEG, but were different from frequency bands measured using EEG from other epidural sites.

Conclusions: Our results demonstrate feasibility in simultaneously measuring both LFP and EEG in awake, behaving rats. Ultimately, this procedure will allow comparison of neurophysiological signals between intracranial and extracranial sites in rats. Moreover, we may implement this technique to compare neurophysiological signals between rats and humans performing analogous probabilistic reward learning tasks, which will help strengthen the validity of this and other translational rodent behavioral models.

Supported By: NIH Grant: UH2 MH109934-01

Keywords: Reward Learning, EEG, medial prefrontal cortex, Animal Models, Translational research

777. Neural Targets of Tacopane Enhanced Reverse-Translated 5-Choice Continuous Performance Test (5C-CPT) Performance in COMT-Genotyped Healthy Adults

Savita Bhakta1, Gregory Light1, Jo Talledo1, Bryan Balvane1, Erica Hughes1, Alexis Alvarez1, Brinda Rana1, Jared Young2, and Neal Swerdlow2

1University of California, San Diego, 2University of California

Background: Failures of pro-cognitive drug trials in schizophrenia (SZ) to detect robust cognitive enhancing effects may reflect the clinical heterogeneity of SZ, and underscore the need to identify the neural targets and reliable biomarkers of such drug effects. We assessed the neural basis for pro-cognitive effects of the catechol-O-methyl transferase (COMT) inhibitor, tacopane, in COMT Val158Met genotyped healthy subjects using an electroencephalogram (EEG)-based 5Choice-Continuous performance test (5C-CPT).

Methods: 27 healthy men and women between the ages 18-35 yrs, homozygous for either Met/Met or Val/Val genotype received placebo and tacopane 200 mg orally across 2 test days separated by 1 week in a double-blind, randomized, counterbalanced, within-subject design. Effects of tacopane on
5C-CPT performance and ERP measures were analyzed using repeated measures ANOVA. Biomarkers predicting tolcapone’s neurocognitive sensitivity were assessed, including SNP rs4680, demographic variables and baseline cognitive performance.

**Results:** Tolcapone was well tolerated, and biologically active. Tolcapone significantly enhanced 5C-CPT D-prime score and frontal P200 amplitude during non-target trials in low baseline 5C-CPT performers while having opposite effects in high baseline performers. Tolcapone-enhanced frontal P200 amplitude was inversely correlated with false alarm rate ($r = -0.4$, $p<0.05$), suggestive of links between neural response and behavior. All neurocognitive effects of tolcapone were independent of COMT rs4680 genotype.

**Conclusions:** Low baseline performers were most sensitive to tolcapone’s pro-cognitive effects. Tolcapone activated frontal electrodes during appropriate response inhibition, consistent with its behavioral effects. These findings suggest a frontal locus of bioactivity for tolcapone and provide strong basis for future biomarker-guided pro-cognitive studies of tolcapone in SZ patients.

**Supported By:** NARSAD, KL2 (Institutional Career Development Award)

**Keywords:** tolcapone, Event Related Potentials, cognitive control, COMT Val/Met, biomarker

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**778. The 5-Choice Continuous Performance Task: A Platform for Examining Markers of Neurophysiological Activity across Species**

Jonathan Brigman
University of New Mexico School of Medicine

**Background:** There is a pressing need for translational tests of cognitive functioning that show similar neurophysiological biomarkers across species. While continuous performance tasks (CPT) are the gold standard for assessing attention and response inhibition clinically, these processes are typically measured in rodents with separate tasks. We integrated a rodent CPT analog (5C-CPT) with electroencephalography (EEG) in the mouse to examine neural activity during attention and response inhibition.

**Methods:** C57BL/6J mice were first trained to initiate and respond for reward to visual stimuli that appeared briefly in 1 of 5 locations on a touch-sensitive screen. Once mice attained stable performance with a short stimulus duration (1.5 sec), mice were fitted with fixed EEG leads resting on the dura. After recovery, trials were added where all 5 response locations were illuminated and mice only received reward for withholding response. EEG activity was recorded during target rewarded (target) and 5-stimuli hold (non-target) trials.

**Results:** Mice acquired stable performance of the 5C-CPT touch-screen variant. Sensitivity index measures showed successful differentiation between target and non-target trials. EEG results showed frontal event-related components had differential responding by trial type, suggesting differential activation of cognitive control processes for trials that required attention only or response inhibition.

**Conclusions:** Here we show the utility of utilizing identical methods for investigating rodent neuronal activity during behavioral tasks that can be used across species. By utilizing clinical EEG methodology we can parse aspects of cognitive control and provide important information about the validity of using rodent models to examine higher order cognitive processes.

**Supported By:** NIH-NIMH 1UH2-MH109168-01

**Keywords:** EEG, Mouse, Touchscreen, Attention

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**779. Cognitive Control Networks in Pediatric Obsessive Compulsive Disorder: Target for Treatment Response?**

Kate Fitzgerald¹, Luke Norman¹, Yanni Liu¹, Gregory Hanna², and Stephan Taylor¹

¹University of Michigan, ²University of Michigan Medical School

**Background:** In youth with OCD, functional alterations of neural networks for cognitive control could reflect a pathological source of OCD symptoms, or an adaptive response that may help patients to reduce symptom severity.

**Methods:** Functional MRI was measured during error and correct trials on the Multi-Source Interference Task in 69 patients with pediatric OCD (half unmedicated) and 72 healthy controls (HC), ages 8-19 years. Error- and interference-processing robustly activated brain regions of relevance for cognitive control, including dorsal anterior cingulate cortex (dACC) and bilateral anterior insula (aI). Effects of group (unmedicated OCD, uOCD; medicated OCD, mOCD; HC), age, performance, interactions and OCD severity (in patients) on activation was examined. A small subset of patients ($n=9$; 16 +/- 1.5 years) were scanned before and after CBT.

**Results:** Dorsal ACC activation to errors was greater for mOCD (but not uOCD) compared to HC, and decreased with age in healthy subjects (and mOCD), but increased with age in uOCD. Greater dACC response to errors associated with better performance and lower OCD severity. Lower OCD severity, particularly in older patients, also associated with greater dACC and left aI activation to interference. Pre- to post-CBT increase in interference-related right lateral prefrontal cortex activation was observed ($p<0.05$, unc) and, at trend-level, associated with lower post-CBT OCD severity ($p=.09$).

**Conclusions:** These findings raise the possibility that compensatory engagement of prefrontal cortical substrate for cognitive control may occur with maturation, medication and CBT to reduce symptom severity in pediatric patients with OCD.
Supported By: R01 MH102242; UL1TR000433; K23MH082176

Keywords: cognitive control, fMRI, pediatric OCD, Developmental trajectories, Treatment

780. CBT-Based Changes in Control and Reward Circuits in Pediatric OCD
Rachel Marsh¹, Emily Steinberg², Paula Yanes-Lukin², Pablo Goldberg², and Moria Rynn³

¹Columbia University, ²The New York State Psychiatric Institute, ³Columbia University and the New York State Psychiatric Institute

Background: Imaging data suggest that the overlapping dorsal and ventral cortico-striato-thalamocortical circuits underlying cognitive control and reward processing are structurally and functionally abnormal in adults with obsessive-compulsive disorder (OCD). Less is known about these circuits in pediatric OCD or how they change following the remission of symptoms.

Methods: We are using HCP-compatible, multimodal MRI sequences to assess the function, connectivity, and organization of control and reward circuits in children and adolescents with OCD before and after CBT with exposure and response prevention. Thus far, we have collected baseline MRI data from 23 unmedicated youth with OCD (12.4 +/- 3.2 years) and 12 matched healthy controls (HCs) and follow-up data from 12 OCD (following 16-20 weeks of CBT) and 6 HC participants (16-20 weeks from baseline scan).

Results: Preliminary fMRI findings point to greater activation of left middle frontal gyrus in HC compared to OCD participants during correct responses to incongruent vs. congruent stimuli on the Simon task at baseline (p=0.005; k=70). Following CBT, increased activation of bilateral fronto-parietal regions (superior, bilateral inferior frontal and precentral gyri, and parietal cortices) was detected in OCD participants from pre to post treatment (p=0.005; k=70).

Conclusions: These preliminary data suggest that the functioning of fronto-parietal control circuits is enhanced following CBT in pediatric OCD. Thus, these circuits may be potential targets for treatment response and the development of novel, early interventions for obsessions and compulsions in youth before OCD onset.

Supported By: NIMH
Keywords: Anxiety, Amygdala, attentional bias, children and adolescence, Threat Response

782. Altered Cognitive Control and Threat Processing Mediates the Relationship between Anxiety Symptoms and Reading Problems in Children
Amy Margolis, Katie Davis, Lauren Thomas, and Rachel Marsh

Columbia University Medical Center

Background: Learning disorders are common in childhood and often comorbid with anxiety disorders or subclinical anxiety. Little is understood about the underlying neural substrates of these comorbid conditions in school-aged children.

Methods: Task-based and resting-state fMRI data were collected from twenty-two children with reading disorder (RD) and 21 typically developing (TD) children who completed tests of reading ability and psychosocial functioning. Groups were compared in whole brain activation on the Simon task and resting-state functional connectivity (RSFC) from amygdalar subregions (basolateral (BLA), centromedial (CMA), and stria terminalis (STR)). We assessed associations of Simon-related activations and RSFC with reading ability and anxiety, and the mediating effects of these brain measures on comorbidity.
Results: During the engagement of cognitive control, children with RD over-engaged left middle frontal gyrus, left posterior medial frontal cortex, and right superior frontal gyrus. Activation mediated the relationship between reading impairment and anxiety. Children with RD also demonstrated increased RSFC from CMA to left frontal pole and from STR to right LOC, which positively predicted anxiety symptoms (p’s<0.05) and partially mediated the relationship between reading impairment and anxiety.

Conclusions: Altered function and connectivity in circuits underlying cognitive control and threat processing mediate the relationship between anxiety symptoms and reading problems in children; such findings might explain the common occurrence of anxiety in children with reading disorder, providing a biological rather than experiential (“I worry because I have a learning problem”) explanation for this comorbidity.

Keywords: Anxiety, Reading disorder, fMRI

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**SYMPOSIUM**

**783. Neurobiological Findings from a Ten-Year Prospective Longitudinal Study of Mood Disorder**

Heather Whalley, Thomas Nickson, Stella Chan, Liana Romaniuk, Stephen Lawrie, and Andrew McIntosh. University of Edinburgh

**Background:** Abnormalities of mood-related brain circuitry are proposed to underlie symptoms of Bipolar disorder (BD) and Major Depressive Disorder (MDD). Whether these abnormalities can distinguish those at greatest risk, how they change over the course of illness development, or how they relate to other risk factors, has yet to be fully determined.

**Methods:** The Scottish Bipolar Family Study (BFS) is a prospective longitudinal imaging study examining young individuals (16-25 years) at high familial risk of mood disorder, along with a group of healthy controls over 10 years. Here we report new data on personality features, neuropsychological data, along with imaging measures and their association with genetic loading.

**Results:** At baseline, the high risk group demonstrated greater depression and cyclothymia versus controls. They also demonstrated decreased directional white matter microstructure (DTI) and increased amygdala activation (which also associated with increased cumulative genetic loading). Separating the high risk group into those who subsequently became unwell (HR-MDD) versus those that remained well (HR-Well); the HR-MDD individuals demonstrated greater depression scores, anxiety and measures of early life events at baseline versus both controls and HR-Well. The HR-MDD group also demonstrated evidence of decreased cognitive flexibility and reduced parahippocampal cortical thickness, and increased insula/prefrontal cortex activation versus controls.

**Conclusions:** These results illustrate behavioural and neural abnormalities in mood-related brain circuitry in individuals at familial risk of mood disorder, with greater differences in those who subsequently become ill. The findings indicate that behavioural and neurobiological differences are associated with increased risk, and some are specifically associated with an impending diagnosis.

**Supported By:** RCPE, Wellcome Trust, European Community’s Seventh Framework Programme.

**Keywords:** bipolar, depression, familial risk, prospective, longitudinal

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**784. Structural Dysconnectivity of Key Cognitive and Emotional Hubs in Young People at High Genetic Risk for Bipolar Disorder**

Philip Mitchell1, Michael Breakspear2, Gloria Roberts3, Alistair Perry2, Andrew Frankland3, Anton Lord4, Vivian Leung3, Ellen Holmes-Preston3, Rhoshel Lenroot3, and Florence Levy3

1The University of New South Wales, 2Queensland Institute of Medical Research, 3University of New South Wales

**Background:** Emerging evidence suggests that psychiatric disorders are associated with disturbances in structural brain networks. Little is known, however, about brain networks in those at high risk of bipolar disorder (BD), with such disturbances carrying substantial predictive and etiological value.

**Methods:** Whole-brain tractography was performed on diffusion-weighted images acquired from 84 unaffected high-risk individuals with at least one first-degree relative with bipolar disorder (HR), 38 young patients with BD and 96 matched controls with no family history of mental illness (CN). We studied structural connectivity differences between these groups, with a focus on highly connected hubs and networks involving emotional centres.

**Results:** HR participants showed lower structural connectivity in two lateralised sub-networks centred upon bilateral inferior frontal gyri and left insular cortex, as well as increased connectivity in a right lateralised limbic sub-network compared to CN subjects. BD was associated with weaker connectivity in a small right-sided sub-network involving connections between fronto-temporal and temporal areas. Although these sub-networks preferentially involved structural hubs, the integrity of the highly connected structural backbone was preserved in both groups. Weaker structural brain networks involving key emotional centres occur in young people at genetic risk of BD and those with established BD. In contrast to other psychiatric disorders such as schizophrenia, the structural core of the brain remains intact despite the local involvement of network hubs.

**Conclusions:** These results add to our understanding of the neurobiological correlates of BD and provide potential for predicting outcomes in young people at high genetic risk for bipolar disorder.
Supported By: Australian National Health and Medical Research Council; and the Landsdowne Foundation

Keywords: Bipolar Disorder, High Risk, Brain Imaging, Connectivity, Inferior frontal gyrus

785. Structural Properties and Connectivity of the Right Inferior Frontal Gyrus in Individuals at Genetic Risk for Bipolar Disorders

Tomas Hajek1, Jason Newport1, Josselin Houenou2, Vladislav Drobini1, Rudolf Uher1, and Martin Alda1
1Dalhousie University, 2INSERM

Background: Relatives of probands with bipolar disorders (BD) show replicated evidence for larger right inferior frontal gyrus (rIFG) volume then controls. Meta-analyses confirmed abnormalities of rIFG functional connectivity and function in subjects with and at risk for BD. Yet, little is known about the structural properties and connectivity of rIFG in participants at genetic risk for BD.

Methods: We measured rIFG cortical thickness and surface area in 61 relatives of bipolar probands and 42 controls without personal or family history of BD. In a subset of 70 participants we collected diffusion tensor imaging and magnetization transfer ratio (MTR) data, to evaluate structural connectivity of uncinate fasciculus, which connects IFG to mesiotemporal structures.

Results: The relatives of bipolar probands demonstrated larger right pars triangularis volume (t(101)=3.42, p=0.0009), surface area (t(101)=3.23, p=0.002) and smaller right uncinate diffusivity than controls (t(68)=-2.2, p=0.03).

Conclusions: We replicated the previous finding of larger rIFG volume in subjects at risk for bipolar disorders in a larger sample using a different method of data analysis. The volumetric changes were localized to pars triangularis and were driven by increased surface area. We also found altered structural connectivity of the right uncinate fasciculus, which was not related to altered myelination. The direction of the volumetric and diffusivity changes in participants at genetic risk for BD was opposite to the most frequently reported direction of findings in participants with fully developed BD. This may indicate dynamic nature of structural changes in BD, which may result from interplay between illness burden and compensatory processes.

Supported By: Canadian Institutes of Health Research, the Nova Scotia Health Research Foundation, the Dalhousie Clinical Research Scholarship to Dr. Hajek.

Keywords: Bipolar Offspring, Structural magnetic resonance imaging, Diffusion Tensor Imaging (DTI), Inferior frontal gyrus, Fronto-limbic Connectivity

786. Brain Networks and Bipolar Disorder: What Can We Learn from Large-Scale Neuroimaging studies?

Josselin Houenou1, Samuel Sarrazin1, Melissa Pauling1, Chantal Henry1, and ENIGMA Bipolar Disorder DTI Working Group2
1INSERM, 2UCLA

Background: Neural models of bipolar disorder (BD) assume that fronto-limbic dysconnectivity lie at the heart of the mechanisms of BD. Both fMRI and diffusion weighted imaging (DWI) studies support the proposed decreased modulation of the limbic reactivity by the frontal regions. This deficient modulation during emotional processes is supposed to then trigger mood instability and switches. However, most of the fMRI and DWI studies used small samples (n<100). Their small sizes increase the risk of false negative results, limit their generalizability and do not allow to study specific subtypes of BD.

Methods: We will here present the results of a series of large-scale multicentric studies we have conducted in BD, including several hundreds of patients with BD and controls who underwent T1 and DWI MRI. We applied several analysis pipelines including gyriification reconstruction, volumetric segmentation, shape analysis and whole brain tractography and segmentation.

Results: Our results tend to decrease the relative importance of fronto-limbic dysconnectivity in patients with BD and highlight alterations in many other networks not yet included in the current models of BD such as the interhemispheric connections and association networks. Further, we also identified markers of altered neurodevelopment such as disrupted gyriification and bundles shape. Finally, some clinical dimensions such as psychotic features were associated with specific disruptions in interhemispheric pathways.

Conclusions: Large-scale neuroimaging structural studies allow a deeper understanding of BD pathophysiology but may also help to reﬁne the psychiatric nosology with the identiﬁcation of neurobiologically-based clinical dimensions.

Supported By: ANR; FRM

Keywords: Diffusion Tensor Imaging (DTI), Structural MRI, Dimensions, Bipolar Disorder

ORAL SESSION
Basic/Translational Neuroscience of Mood Disorders
Saturday, May 20, 2017 - 3:00 PM - 5:00 PM
Aqua 310 AB
Chair: Susannah Tye

787. Xenon in Sub-Anesthetic Doses for Treatment of Major Depression: A Proof-of-Concept Placebo-Controlled Pilot Study

Lyubomir Aftanas1, Olga Akhmetova2, Ivan Brack2, Konstantin Danilenko2, Alexander Khabarov2, and Ekaterina Nikolenko2
1Scientific Research Institute of Physiology & Basic Medicine, Novosibirsk State University, Novosibirsk, Russia, 2Scientific Research Institute of Physiology & Basic Medicine, Novosibirsk, Russia

Background: We hypothesized that like ketamine, the general anesthetic and N-methyl-D-aspartate receptor antagonist
xenon (Xe) inhaled in sub-anesthetic doses may be an acting treatment for Major Depression Disorder (MDD).

**Methods:** In this randomized, single-blind, placebo-controlled, parallel-group study, 30 patients manifesting moderate or severe MDD were randomly assigned to 10 daily 15 min inhalation session either of 25% Xe/30% oxygen/45% nitrogen (treatment group, n=15) or 70% nitrogen/30% oxygen (placebo control, n=15). The primary endpoints were changes on the Beck Depression Inventory (BDI-II) scale.

**Results:** Each 15 min Xe treatment session was performed at a median inspiratory concentration of 17%, while a peak Xe concentration (at a median of 24%) was maintained for 5 min. The treatment was discontinued in 3 patients from the placebo and 1 patient from the Xe groups for emotional discomfort and claustrophobia. No adverse events occurred. The treatment response was indexed by marked decrease of negative affect. According to the 2-way ANOVA with Group (2: Xe, Placebo) as the between factor and TIME (2: before and after treatment) as the repeated measures factor the 10 days inhalation sessions significantly reduced BDI-II scores in both groups (TIME: F(1, 24) = 47.01, pG-G= 0.001). However, the 2-way GroupTIME interaction (F(1, 24) = 17.46, pG-G= 0.001) followed by planned comparisons specify significantly more robust antidepressant effect of Xe (at p <.001).

**Conclusions:** Supporting our preliminary observation the findings provide the first placebo-controlled evidence that Xe devoid of ketamine’s toxicity sequelae may have marked antidepressant effects in patients with MDD.

**Supported By:** The Russian Science Foundation grant #16-15-00128 to Lyubomir Aftanas; The Russian Academy of Science Program 2015-2017 "Affective neuroscience" to Lyubomir Aftanas

**Keywords:** Major Depressive Disorder (MDD), Xenon, NMDA antagonists, Novel treatments

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788. **Local Translation of Synaptic Proteins Supports Plasticity Specifically at Distal Hippocampal Synapses**

Matthew Klein1, Adina Buxbaum2, Thomas Younts3, Jonathan Aow2, Carmen Cobo4, Roberto Malinow2, Pablo Castillo4, and Bryen Jordan4

1Department of Psychiatry, Johns Hopkins University School of Medicine, 2JHU School of Medicine, 3Neuroscience, UCSD, 4Neuroscience, Albert Einstein College of Medicine

**Background:** The localization of mRNAs to synapses is a fundamental process underlying synaptic plasticity, the cellular correlate of learning and memory. Consequently, abnormal local gene expression is associated with a variety of neuropsychiatric disorders, including Fragile X Syndrome, Autism, and Alzheimer’s. While the existence of local translation in neurons is well documented, how synaptic protein synthesis supports plasticity throughout the dendritic arbor remains unknown. Here, we show that loss of the RNA binding protein Sam68 results in reduced synaptic protein synthesis, along with decreased synaptic plasticity specifically at distal hippocampal synapses.

**Methods:** Synaptic plasticity and translation were assessed in two models; Sam68 knock out mice, or mice subjected to virus-mediated knockdown of Sam68. In acute hippocampal slices, we performed electrophysiology, 2-photon imaging single molecule FISH, and fluorescent non-canonical amino acid targeting.

**Results:** Knock-down of Sam68 resulted in decreased localization of mRNA to distal hippocampal synapses, which correlated with decreased translation of synaptic protein. No difference was observed in somatic mRNA or protein levels. Surprisingly, mGluR-mediated long term depression was reduced specifically at distal synapses, but not at synapses proximal to the neuronal soma.

**Conclusions:** Here, in an intact neuronal circuit, we provide the first examples of a specific deficit in local synaptic plasticity arising from decreased synaptic translation. Our results demonstrate the crucial role of Sam68 in localizing gene expression to synapses, which allows for restricted expression of synaptic plasticity. Finally, we provide a model linking disruptions in protein synthesis observed in syndromic forms of Autism and Intellectual Disability to cognitive dysfunction.

**Supported By:** NIMH-F31-NS08, 300; NIGMS-T32-GM007288; NIMH-R01-MH049159

**Keywords:** local translation, synaptic plasticity, mRNA-localizing binding proteins, Autism Spectrum Disorder

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789. **A Novel Mast Cell-Vagal Network Regulates Chronic Depression and Anxiety-Like Behaviors after Transient Gastric Irritation**

Zachary Cordner1, Liangsheng Liu2, Timothy Moran2, Qian Li3, Aditi Bhargave3, Kellie Tamashiro2, and Pankaj Pasricha2

1Department of Psychiatry, Johns Hopkins University School of Medicine, 2Johns Hopkins University School of Medicine, 3University of California San Francisco

**Background:** Functional bowel disorders including functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common causes of morbidity with a lifetime prevalence of 15-20%, and nearly all affected individuals have co-occurring features of depression or anxiety. While etiology is largely unknown, a commonly held belief is that FD and IBS represent somatic manifestations of underlying psychiatric disorders. However, most studies ignore the complex, bidirectional nature of the gut-brain axis and the possibility that gastrointestinal irritation could cause chronic somatic and psychiatric symptoms.

**Methods:** We induced mild, transient gastric irritation in neonatal male rats by oral gavage of 0.1% iodoacetamide once a day for 7 days. As adults, depression and anxiety-like behaviors were assessed in the open field, forced swim, and sucrose preference tests. Vagal nerve single-fiber responses to graded gastric distention were recorded. Stomach tissue
was collected for mast cell staining. In separate cohorts, the effects of subdiaphragmatic vagotomy and oral treatment with the mast cell stabilizer ketotifen were determined.

**Results:** Rats exposed to transient neonatal irritation displayed prominent depressive-like and anxiety-like behavior, increased vagal activity in response to gastric distension, and gastric mast cell activation. Both subdiaphragmatic vagotomy and treatment with ketotifen during adulthood completely reversed the depressive and anxiety-like phenotype, normalized vagal activity to gastric distension, and normalized mast cell number.

**Conclusions:** The model presented here recapitulates many of the psychiatric and somatic features of Functional Dyspepsia and suggests that transient gastric irritation may result in chronic depression, anxiety, and pain hypersensitivity-like behaviors that are regulated by a novel mast cell-vagal network.

**Supported By:** NIH R01DK097518

**Keywords:** Depression, Anxiety, Animal Models, Behavior, Vagus

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**790. Ketamine Exerts NMDAR Inhibition-Independent Antidepressant Actions via Its Hydroxynorketamine Metabolites**

Panos Zanos1, Ruin Moaddel2, Patrick Morris3, Polynymia Georgiou4, Jonathan Fischell5, Greg Elmer6, Manickavasagorn Alkondon7, Peixiong Yuan8, Heather Pribut9, Nagendra Singh10, Katina Dossou2, Yuhong Fang3, Xi-Ping Huang3, Cheryl Mayo6, Irving Wainer10, Edson Albuquerque7, Scott Thompson11, Craig Thomas9, Carlos Zarate12, and Todd Gould13

1University of Maryland, Baltimore, School of Medicine, 2Biomedical Research Center, National Institute on Aging, National Institutes of Health, 3Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, 4Department of Psychiatry, University of Maryland School of Medicine, 5University of Maryland, Baltimore, School of Physiology, 6Maryland Psychiatric Research Center, University of Maryland School of Medicine, 7Department of Epidemiology and Public Health, Division of Translational Toxicology, University of Maryland School of Medicine, 8Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, 9NIMH Psychoactive Drug Screening Program, Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry, University of North Carolina Chapel Hill Medical School, Chapel Hill, 10Mitchell Woods Pharmaceuticals, 11Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, 12National Institute of Mental Health, 13University of Maryland Baltimore

**Background:** In contrast to the currently-available antidepressants, a single administration of ketamine results in a rapid and sustained improvement of core depressive symptoms in patients. However, clinical use of ketamine is limited due to its serious side effects. Although ketamine thought to exert its antidepressant actions via blocking the NMDAR, other NMDAR antagonists are not antidepressants, thus we hypothesized that ketamine’s antidepressant actions might be mediated by its metabolites.

**Methods:** Using mouse tests we assessed the antidepressant efficacy of ketamine’s enantiomers and its hydroxynorketamine (HNK) metabolites. We also performed in vivo electroencephalogram, in vitro field excitatory post-synaptic potential (fEPSP) measurements and western blots for AMPA receptor subunits. Side effects were also assessed.

**Results:** Our experiments reveal that NMDAR inhibition is not responsible for the unique antidepressant actions of ketamine since MK-801 (another NMDAR channel blocker) does not exert the sustained ketamine-like effects and the (R)-ketamine enantiomer (~4-fold lower affinity for the NMDAR), exerts superior antidepressant responses compared to (S)-ketamine. We demonstrated that production of the (2S,6S;2R,6R)-HNK metabolite is essential for ketamine’s sustained antidepressant effects. Importantly, the (2R,6R)-HNK enantiomer exerts behavioral, electroencephalographic, electrophysiological and cellular actions, which can explain ketamine’s antidepressant actions. We also demonstrated that AMPA receptor activation is critical for (2R,6R)-HNK’s effects. This metabolite did not exert ketamine-associated side effects.

**Conclusions:** Our results indicate a novel mechanism mediating ketamine’s unique antidepressant properties, which is independent of NMDAR inhibition. Considering the lack of side effects, these findings have relevance for the development of next generation, rapid-acting antidepressants.

**Supported By:** NIMH grants: MH099345 and MH107615 to T. D.G. and MH086828 to S.M.T

**Keywords:** Ketamine, Antidepressant, Metabolism, NMDA Receptor, AMPA

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**791. Molecular Drivers of Neural Circuitry of Resilience**

Rainbo Hultman, Stephen Mague, Cameron Blount, and Kafui Dzirasa

Duke University Medical Center

**Background:** Neural circuit disruptions have been increasingly appreciated as contributing directly to psychiatric dysfunction, making the identification of such disruptions extremely promising as therapeutic targets. Identifying molecular contributors to specific neural circuit activity may provide a more promising route to efficacious drugs that target specific circuit-level causes of psychiatric dysfunction. In order to dissect the ways in which gene, cells, and neural circuits coordinate to depressive-like response to chronic stress, we employed a multidisciplinary approach using in vivo neurophysiology and RNA-Seq in a mouse model of chronic social stress.

**Methods:** Using in vivo neurophysiology in freely behaving mice, we recorded an endophenotype of stress-susceptibility: pre-frontal cortex 2-7Hz oscillatory activity. We then measured
the reactivity of this neural signature in a preclinical model of the ‘aggressive faces’ task. Finally, prefrontal cortex tissue was microdissected and gene expression was detected according to neural circuit activity using RNA-Seq.

**Results:** We found that gene pathways associated with the mitochondrial complex ii were upregulated in animals with resilience-like neural biomarker prior to stress exposure (n=12). We then used AAV manipulations to demonstrate that upregulation of this pathway was sufficient to confer resilience to chronic social defeat stress (one-tailed t-test p=.02; n=8 per group).

**Conclusions:** Here we demonstrate that combining in vivo neurophysiology and Next Generation Sequencing can be a powerful approach for the identification of molecular drivers of specific neural circuit function with regard to stress-related pathology. Applying such approaches more widely will be essential for the development of circuit-based psychopharmacotherapeutics.

**Keywords:** Resilience, Prefrontal Cortex, Chronic Stress, neural circuits, novel drug targets

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**792. Tired and MISCONNECTED: A Breakdown of Brain Modularity following Sleep Deprivation**

Eti Ben Simon, Nir Lahav, Ron Shamir, Talma Hendler, and Adi Maron-Katz

1UC Berkeley, 2Bar-Ilan Univ, 3Blavatnik School of Computer Science, Tel-Aviv University, 4Tel Aviv Sourasky Medical Center, 5Stanford University, Department of Psychiatry and Behavioral Sciences

**Background:** Sleep deprivation (SD) critically affects a range of cognitive and affective functions, typically assessed during task performance. Whether such impairments stem from changes to the brain’s intrinsic functional connectivity remains largely unknown.

**Methods:** We applied a graph based analysis on resting-state functional connectivity networks derived from fMRI data of 18 participants, recorded during both sleep-rested and sleep-deprived states. In each state we examined the community structure of the network and its relation to behavior.

**Results:** Our findings point to a profound reduction in network modularity without sleep, evident in the limbic, default-mode, salience and fronto-parietal modules. As hypothesized, these changes were found to be associated with behavioral and neural impairments elicited by SD: reduction in thalamocortical connectivity was associated with decreased task performance, an increase in limbic module density was predictive of stronger amygdala activation in a subsequent task and shifts in frontal hub lateralization were associated with increased negative mood.

**Conclusions:** Altogether, these results portray the profound effects of SD on the intrinsic functional organization of the brain, leading to a loss of functional segregation and a shift towards a more random-like network. These changes further reflect cognitive and affective impairments, already detected in the spontaneous activity of the sleep-deprived brain.

**Keywords:** Sleep Deprivation, Functional MRI, graph theory, Functional connectivity, Mood

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**793. Camp-Dependent and NMDAR-Independent Action of Ketamine in a Cellular Model System**

Nathan Wray, Jeff Schappi, Harinder Singh, and Mark Rasenick

U. Illinois Chicago College of Medicine

**Background:** Previous studies demonstrated that all extant classes of antidepressants increase coupling between the G protein, Gαs and adenylyl cyclase, resulting in persistent cAMP elevation. This is apparently due to Gαs being released from constraints of a lipid-raft environment to cholesterol-poor regions of the plasma membrane. Peripheral tissue and postmortem brain from depressed human subjects show a greater proportion of Gαs in lipid rafts.

**Methods:** C6 glioma cells or primary astrocytes were treated with ketamine, harvested and lipid-raft Gαs was determined. C6 cells expressing GFP-Gαs were treated similarly with ketamine and the mobility of Gαs was determined by Fluorescence Recovery after Photobleaching (FRAP). BDNF, CREB and pCREB were also quantified after immunoblotting.

**Results:** Brief (15-minute) ketamine treatment evoked the biochemical hallmark (translocation of Gαs from lipid rafts) seen after prolonged treatment with several species of antidepressant drugs. This is not mimicked by other NMDA antagonists, suggesting an additional site for ketamine action. Ketamine increased functional coupling of Gαs and adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). This phosphorylated cAMP-response-element-binding-protein (CREB), which promoted BDNF synthesis. These events were dependent on cAMP as Rp-cAMPS attenuated BDNF expression levels. Furthermore, BDNF expression was increased in primary astrocytes after ketamine treatment.

**Conclusions:** These results reveal a novel antidepressant mechanism in glia following a brief ketamine treatment that may contribute to ketamine’s antidepressant effect. Furthermore, the translocation of GFP-Gαs produced by ketamine and all tested compounds with antidepressant activity might serve as a useful platform for identifying compounds with potential antidepressant activity and for predicting clinical response.

**Supported By:** NIH R01 AT009169; VA Merit BX001149

**Keywords:** GPCR, BDNF, cAMP, Antidepressants, lipid raft

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**794. Mechanism of Action of Novel Modulators of Serotonin, Dopamine, and Mu Opiate Receptors for Treatment of Mood Disorders**

Gretchen Snyder, Peng Li, Wei Yao, Stephanie Cruz, Lawrence Wennogle, Sharon Mates, and Robert Davis

Intra-Cellular Therapies, Inc
Background: A series of novel compounds has been discovered that bind 5-HT2A, D1 and mu opiate receptors. This series is exemplified by ITI-333, which possesses low nanomolar affinity for 5-HT2A, D1 and mu opioid receptors with Ki values of 8.3nM, 50nM and 11nM, respectively. Here, we report the pharmacological profile of ITI-333.

Methods: The pharmacological profile of ITI-333 was explored using in vitro receptor binding and cell-based functional assays and in vivo tests of functional activity at 5-HT2A, D1, D2, and mu opioid receptors, including DOI-induced head twitch, morphine-induced hyperactivity, western blotting measurements of brain phosphoprotein levels (tyrosine hydroxylase and GluN2B), and blockade of morphine activity in the classical mouse tail flick assay of pain.

Results: ITI-333 exhibits oral activity and excellent metabolic stability in animals. Oral administration of ITI-333 potently blocked DOI-induced head twitches in mice (EC50 = 0.23mg/kg, p.o.) indicating strong functional activity as a 5-HT2A antagonist. ITI-333 did not disrupt striatal dopamine neurotransmission at doses tested, as indicated by a lack of effect on striatal tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis. ITI-333 (0.3mg/kg, p.o.) displayed potent morphine antagonism in vivo, blocking morphine-induced hyperactivity and morphine-induced analgesia in mice at dose levels comparable to its 5-HT2A receptor effects (i.e., 0.1mg/kg and above, p.o.).

Conclusions: The unique pharmacological profile of ITI-333—including potent 5-HT2A antagonism, D1 activity and morphine antagonism—is predicted to translate into utility for addressing symptoms of mood disorders and opiate abuse, particularly in patients with both substance use disorders and depression.

Supported By: Intra-Cellular Therapies Inc

Keywords: serotonin 2A receptor, bipolar disorder, mu opioid receptor, morphine, dopamine D1 receptor

ORAL SESSION - MIXED TOPICS #2
Saturday, May 20, 2017 - 3:00 PM - 5:00 PM
Aquarius 311 AB
Chair: Alik Widge

795. White Matter Microstructure in Anorexia Nervosa: State-Dependent and Potentially Heritable Differences

Amy Miles1, Allan Kaplan1, Mallar Chakravarty2, and Aristotle Voinikos1

1University of Toronto, Centre for Addiction and Mental Health, 2McGill University, Douglas Institute

Background: Anorexia Nervosa (AN) is a highly heritable and frequently chronic psychiatric illness, the neural correlates of which are poorly understood. By comparing structural measures across underweight (uAN) and weight-recovered (recAN) subjects, their unaffected sisters (sibAN), and unrelated controls (HC), this study aims to identify and discriminate between potentially heritable differences and those attributable to acute malnutrition.

Methods: DTI with 60 gradient directions was performed on a 3T GE scanner, and TBSS was used to assess brain-wide white matter microstructure. Analyses of covariance and multiple regression were used to examine group differences and their functional correlates, respectively.

Results: To date, 79 women (22 uAN, 23 recAN, 12 sibAN, 22 HC) have been imaged. After correcting for multiple comparisons, significant group differences in mean diffusivity (MD), an index of axonal disorganization, were observed in 8.1% of all white matter voxels. Of these differences, 18.5% were state-dependent (uAN > HC), 35.8% were phenotype-dependent (uAN, recAN > HC), and 45.7% showed evidence of heritability (uAN, recAN, sibAN > HC). State-dependent differences were observed in posterior and inferior, association and projection tracts; phenotype-dependent differences were observed throughout the Corpus Callosum; and potentially heritable differences were observed in anterior and superior, association and projection tracts. Mean diffusivity along these tracts was significantly associated with emotion dysregulation and interoceptive defects, drive for thinness and body dissatisfaction, and perfectionism and harm avoidance, respectively.

Conclusions: Altered white matter microstructure indicative of axonal disorganization may confer vulnerability to Anorexia Nervosa or contribute to symptom exacerbation post onset.

Supported By: CAMH AFP Innovation Grant

Keywords: Anorexia Nervosa, White Matter Microstructure, Diffusion Tensor Imaging (DTI), Tract Based Spatial Statistics (TBSS)

796. The Influence of Childhood Trauma, Major Depressive Disorder and Telomere Length on HIV-Associated Neurocognitive Disorders

Jacqueline Womersley, Georgina Spies, Stefanie Malan-Muller, Gerardus Tromp, Soraya Seedat, and Sian Hemmings

University of Stellenbosch

Background: The prevalence of HIV-associated neurocognitive disorders (HAND) continues to increase despite improvement in access to antiretroviral medication. Research suggests that stress-related psychiatric conditions and depression are associated with HIV disease progression and the development of neurocognitive impairment. This relationship is particularly relevant to sub-Saharan Africa, where HIV is most prevalent, as the combination of HIV and stress-related psychiatric conditions essentially produces a double burden of disease. We sought to examine whether telomere length attrition, a marker of biological aging, independently associated with childhood trauma, depression and HAND, may act as a biological correlate mediating the relationship between HAND and psychological stress.

Methods: HIV positive (n=133) and negative women (n=150) underwent a battery of neuropsychological tests to measure cognitive function, depression and childhood trauma. Quantitative polymerase chain reaction using primers specific
to telomeric repeats and the reference gene human β-globin was performed on DNA extracted from peripheral blood mononuclear cells. Data were analysed using generalised linear models.

**Results:** HIV seropositivity was strongly predictive of reduced telomere length. Furthermore, including the interaction between childhood trauma and HIV status in the statistical model explained significantly more of the variance in telomere length ($p=0.035$). HIV status, childhood trauma, depression and telomere length did not affect cognitive function. However, including the interaction between depression and telomere length explained significantly more of the variance in cognitive function ($p=0.025$).

**Conclusions:** Our data suggest that HIV decreases telomere length and that the interaction between biological measures and psychological ill health may be important in influencing cognitive status.

**Supported By:** South African Research Chair in Post Traumatic Stress Disorder hosted by Stellenbosch University, funded by the South African Department of Science and Technology and administered by the South African National Research Foundation

**Keywords:** HIV, Childhood Trauma, Depression, Telomere Length, HIV-associated neurocognitive disorders

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**797. FKBP5 Variant rs3800373 Alters FKBP5 RNA Secondary Structure and Prevents Stress-Induced microRNA-320a Downregulation of FKBP5, Resulting in Glucocorticoid Resistance and Increased Vulnerability to Chronic Posttraumatic Pain**

**Sarah Linnastraedt**, Kyle Riker, Katrina Kutchko, Lela Lackey, Michael Kurz, Christopher Lewandowski, Claire Pearson, Phyllis Hendry, Alain Laederach, and Samuel McLean

1University of North Carolina, 2University of Alabama Birmingham, 3Henry Ford Hospital, 4Detroit Receiving Hospital, 5University of Florida College of Medicine - Jacksonville, 6University of North Carolina at Chapel Hill

**Background:** We previously found that (1) glucocorticoid receptor co-chaperone FKBP5 minor allele genetic variant rs3800373 predicts worse chronic posttraumatic pain (CPTP) and (2) microRNA-320a directly regulates FKBP5 RNA and predicts CPTP in a stress-dependent manner. In this study we evaluated the hypothesis, based on in silico data, that rs3800373 alters miR-320a binding.

**Methods:** Using a prospective observational cohort of African Americans presenting to the emergency department after motor vehicle collision, we (1) validated the association between rs3800373 and CPTP ($n=907$), (2) used total RNA- and microRNA-seq data ($n=96$ and 172, respectively) to evaluate associations between FKBP5, Glucocorticoid Receptor (NR3C1), and miR-320a expression among individuals with and without the minor allele, and (3) evaluated miR-320a/FKBP5 RNA binding in vitro and in vivo.

**Results:** Individuals with one or more copies of the rs3800373 minor allele experienced greater CPTP. Among such individuals, FKBP5 and NR3C1 expression were highly correlated ($r=0.67, p=9x10^{-6}$), suggesting glucocorticoid resistance, and (unlike those without the minor allele) no negative correlation between miR-320a and FKBP5 RNA was observed, suggesting escape from miR-320a regulation. Allele-specific miR-320a binding was supported by luciferase reporter assays, and in vivo SHAPE data suggested that differences in miR-320a binding are due to allele-specific changes in RNA secondary structure.

**Conclusions:** The FKBP5 rs3800373 risk variant prevents stress-induced miR-320a downregulation of FKBP5, resulting in glucocorticoid resistance and increased vulnerability to chronic posttraumatic pain.

**Supported By:** R01 AR060852, Mayday Fund, Future Leader in Pain Grant

**Keywords:** FKBP5, mechanisms, microRNA, Trauma Exposure, chronic pain

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**798. A Role for mTOR Dependent Neuronal Autophagy in Dendritic Spine Pathology in Autism**

Guomei Tang and David Sulzer

Columbia University

**Background:** Dendritic spines are primary sites where neurons receive and integrate excitatory synaptic inputs. While abnormalities of dendritic spines are implicated in autism spectrum disorders (ASDs), the underlying mechanisms remain unclear. One molecular candidate is the mammalian target of rapamycin (mTOR), a kinase that regulates protein homeostasis by promoting protein synthesis and inhibiting macroautophagy (autophagy thereafter), a degradation process whereby cellular proteins and organelles are engulfed by autophagosomes, digested in lysosomes, and recycled to sustain cellular metabolism.

**Methods:** We examined mTOR-autophagy activities and dendritic spine morphology during early postnatal development in control and autism postmortem human brains. The relationship between dysregulated mTOR-autophagy, autistic-like dendritic spine pathology and social behaviors was determined in mouse models of tuberous sclerosis complex (TSC) and in mice lack of essential autophagy gene ATG7 (Atg7 Knockout) mice.

**Results:** mTOR dis inhibition in TSC mutant mice causes impaired autophagy, increased dendritic spines, and autistic like social behaviors. Autophagy deficiency blocks dendritic spine pruning, a process that eliminates excess synaptic connections on cortical projection neurons during early postnatal development. Spine pathology and autistic behaviors can be reversed by mTOR inhibitor rapamycin in TSC mutant mice, but not in TSC mutant Atg7 knockout mice. We confirmed this link between mTOR-autophagy and synaptic pruning in autism postmortem brains, in which increased dendritic spine density negatively correlates with impaired mTOR-autophagy.

**Conclusions:** Our studies provide the first evidence that mTOR-autophagy is implicated in the dendritic spine pathology in autism. Further study of the mechanisms that autophagy regulates spine morphogenesis may suggest novel therapeutic targets.
Supported By: Simons Foundation  
Keywords: Autism Spectrum Disorder, dendritic spine, mTOR, autophagy, Pruning

799. Behavioral and Molecular Effects of Putative OCD Risk Gene BTBD3  
Summer Thompson1, Emily Ho1, Monica Morais2, Madeline Klinger3, Amanda Welch1, Marcia Ramaker1, James Knowles4, João Bessa2, Jared Young1, Nuno Sousa1, and Stephanie Dulawa1  
UCSD, University of Minho, The University of Chicago, USC

Background: BTBD3 is genome-wide significant for obsessive-compulsive disorder (OCD) in the trio portion of the first OCD GWAS. However, the function of BTBD3 is largely unknown. Here we studied effects of BTBD3 on OCD-related behaviors and neuronal morphology in mice.  
Methods: Wild-type (WT), heterozygous (HT) and knockout (KO) mice were assessed for effects of BTBD3 on behavior. Separate mice underwent chronic treatment with 10 mg/kg/day fluoxetine, 20 mg/kg/day desipramine, or vehicle then were assessed for behavioral effects. BTBD3 mouse brains underwent Golgi-Cox staining to assess dendritic morphology. Lastly, P21 WT mice received viral infusions of BTBD3-shRNA into hippocampus and were assessed for behavioral effects four weeks later. Effects were assessed using ANOVAs (alpha=0.05) except barbering incidence, which was assessed using chi-square and survival analyses.  
Results: Open field (n=11-34/genotype/sex): BTBD3 KO mice were hyperactive. HT and KO mice showed reduced rearing. Dig test (n=13-21/genotype/sex): KO mice exhibited reduced digging. Nest-building (n=12/genotype/sex): KO mice had impaired nest-building. Wheel-running (n=9-10/genotype/sex): KO mice exhibited compulsive wheel-running. Cognition (n=11-18/genotype): HT and KO mice were less impulsive in go/no-go and KO mice had reduced accuracy in probabilistic learning. Barbering (n=12-19/genotype/sex/drug): HT and KO mice barbered more than WT. Fluoxetine but not desipramine reduced barbering in WT and HT but not KO mice. Hippocampal BTBD3 knockdown (n=7-8/virus): Knockdown mice had impaired nest-building. Dendritic Morphology (n=5-6/genotype): KO mice have increased spine density and decreased apical branching in anterior cingulate layer II/III neurons.  
Conclusions: BTBD3 expression modulates behaviors relevant to OCD and dendritic morphology. Hippocampus may be important for BTBD3’s role in behavior.  
Supported By: R21-MH104829; R01-MH099248; NARSAD; Norton Gerali Foundation  
Keywords: Obsessive Compulsive Disorder (OCD), Animal Models, Animal Behavior, Compulsivity

800. Default Mode Network Abnormalities in Antipsychotic-Naïve Schizotypal Personality Disorder  
Erin Hazlett, Cheuk Tang, Edmund Wong, Caitlin Kelliher, Chi Chan, Justin Penner, Philip Szeszko, Mercedes Perez-Rodriguez, Daniel Rosell, Antonia New, Panos Roussos, and Larry Siever  
Icahn School of Medicine at Mt. Sinai

Background: Studying schizotypal personality disorder (SPD) can further our understanding of the psychopathology of schizophrenia given empirical evidence that SPD subjects show similar, but attenuated cognitive/emotional deficits and brain abnormalities. Although several studies reported default mode network (DMN) abnormalities in schizophrenia, there is a paucity of neuroimaging work in SPD examining this network despite the advantage of being able to study psychotropic drug-naïve participants.  
Methods: DMN functional connectivity was examined in a large demographically-matched community sample of 57 psychotropic medication-naïve SPD participants and 54 healthy controls (HCs, without any Axis I or II diagnoses). All participants received a structured-diagnostic interview and 3T resting state functional magnetic resonance (fMRI) scan. Independent component analysis was used to analyze DMN functional connectivity with an emphasis on the prefrontal cortex and superior temporal gyrus (STG), key regions known to play a role in the neurobiology of schizophrenia-spectrum disorders.  
Results: Compared with the HCs, SPD participants had greater functional connectivity in prefrontal cortical regions, including the superior and medial frontal gyrus, as well as bilateral STG. These findings are consistent with prior work reporting greater STG activation during auditory processing (Dickey et al 2008) and compensatory frontal lobe functioning in SPD (e.g., Hazlett et al 2008).  
Conclusions: Our findings are consistent with the hypothesis that regions comprising the DMN and its associated connectivity demonstrate greater activation in SPD and may therefore, mitigate against the emergence of psychosis. Clinical correlations with the Schizotypal Personality Questionnaire will also be presented.  
Supported By: VA Merit Awards to LJS and EAH.  
Keywords: Schizotypal Personality Disorder, Resting state fMRI, Prefrontal Cortex, Superior temporal gyrus, Magnetic resonance imaging

801. Developmental Nicotine Exposure Induces Persistent Alterations in Accumbens Glutamatergic Circuitry  
Cassandra Gipson, Gregory Powell, Armani Del Franco, Holter Mike, Garcia Raul, Vannan Annika, and Janet Neisewander  
Arizona State University

Background: Developmental nicotine exposure (DNE) is used to model human smoking during pregnancy, and has been shown to cause alterations in glutamate receptors, dendritic morphology, and neuronal function as well as increase nicotine (NIC) self-administration in adult rats. The underlying neurobiological mechanisms leading to increased nicotine addiction vulnerability following DNE, however, are unknown.  
Methods: mRNA expression of proteins including glutamate receptors (AMPA [GluA1, GluA2] and NMDA [GluN2A, GluN2B]) and transporters (GLT-1) was examined. Pregnant rats were implanted with an osmotic minipump on gestational day 5,
802. Cholesterol Efflux Mediates the Relationship between Suicide Risk and Unesterified Cholesterol

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Background: While the link between suicide and cholesterol is well established the etiology of this association remains unknown. We used a family-based approach to decompose the shared covariance between traits into genetic and environmental components, as well as to investigate the mediating role of cholesterol efflux capacity (CEC) on this relationship.

Methods: In a sample of 552 Mexican American individuals from extended pedigrees we calculated the standardized genetic covariances between 23 lipid classes (from 10 plasma) and attempted suicide. Multilevel mediation analysis was used to investigate the roles of plasma-based CEC (non-ABCA1, and ABCA1-specific) and Lecithin:cholesterol acyltransferase (LCAT) respectively, so we investigated the relationships in the data. Only UC and ABCA1-specific CEC (rhog = −0.64, p = 1.38x10−06) shared significant genetic overlap. Moreover, the relationship between free cholesterol and attempted suicide was significantly mediated by ABCA1-specific CEC (β = 0.07, p = 0.035).

Conclusions: While alterations in cholesterol levels have been previously associated with attempted suicide the present study is the first to suggest that this association is due, at least in part, to shared genetic influences. In addition the results of this study suggest that cholesterol efflux, an initial step in the process of reverse cholesterol transport, may be key to the association between free cholesterol and attempted suicide.

Supported By: MH078143; MH078111; MH083824; MH059490

Keywords: Suicide, lipids, cholesterol, family study, Genetics
be context-independent in children. These results differ from previous findings in adults suggesting context-dependency of extinction. These findings may have implications for adaptations of behavioural interventions for use in children, and for the development of stress-related disorders.

Supported By: Wayne State University Department of Pharmacy Practice, American Cancer Society, NIH National Institute of Mental Health

Keywords: Fear, Fear Extinction, Fear conditioning, Virtual Reality, context

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804. Effects of Acute Δ9-ΤΕΤΡΑΗΔΡΟΚΑΝΝΑΒΙΝΙΟΛ on Resting-State Functional Connectivity in Fear-Related Neural Circuity

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Background: An acute dose of Δ9-tetrahydrocannabininol (THC) can alter threat perception and enhance suppression of conditioned fear responses by modulating fear-related brain circuitry, including the ventromedial prefrontal cortex (vmPFC), hippocampus (HPC), and amygdala (AMYG). It remains unknown if these THC-induced changes in fear-related brain function exist at baseline or “at rest,” in the absence of fear/threat-related provocation and outside the context of task demands. Therefore the primary aim of the present study was to investigate whether an acute dose of THC alters functional connectivity patterns within vmPFC-HPC-AMYG fear-circuit in healthy adult volunteers during resting-state.

Methods: We used resting-state functional magnetic resonance imaging (RS-fMRI) in a randomized, double-blind, placebo-controlled, between-subjects design to compare acute pharmacological effects of THC (7.5mg vs. placebo [PBO]) on RS-functional connectivity (RS-FC) within fear-related circuitry in 77 healthy adult volunteers (THC = 40; PBO = 37). RS-FC was analyzed using an ROI-ROI approach with vmPFC, bilateral HPC, and bilateral AMYG as seed regions. We assessed RS-FC between our ROIs using two complementary approaches: 1) static FC (correlations between ROIs across the entire scan); and 2) dynamic FC (sliding window correlation time series’ variance) to measure time-varying changes in ROI-ROI FC.

Results: Compared to PBO, THC decreased left-right HPC static rs-FC, but increased dynamic rs-FC between left-right HPC, an increased right HPC-left AMYG (ps < 0.05). 

Conclusions: An acute dose of THC modulates both static and dynamic rs-FC networks critical to emotional memory in fear circuitry at rest.

Supported By: NIH R21MH093917; NIH UL1RR024986 and UL1RR029879; NIH K01MH101123

Keywords: Cannabinoid, Resting state functional connectivity, fear neurocircuitry

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805. Associations between Heart Rate Variability and Emotion Regulation among Adolescents with Psychiatric Disorders

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Background: Heart rate variability (HRV) has been reported to be a good indicator of self-regulation abilities and of states of psychological stress. However, high frequency (HF) HRV and very low frequency (VLF) HRV are rarely investigated among psychiatric patients. Our goal is to examine how high frequency HRV and very low frequency HRV at rest are associated with anxiety and emotion regulation among adolescents with psychiatric disorders.

Methods: Eighteen adolescents (Mage = 15.1 years, SDage = 1.41) with various psychiatric disorders in a psychiatric day care unit took part in this study. They wore a t-shirt with integrated sensors recording their electrocardiogram during a two hours session and filled in questionnaires on anxiety (State-Trait Anxiety Inventory; STAI) and on emotion regulation (Cognitive Emotion Regulation Questionnaire; CERQ).

Results: First, VLF was significantly linked to two dimensions of the CERQ: Refocus on planning and Blaming others, ρ(13) = .77, p < .001 and ρ(14) = .56, p < .05, respectively. Second, HF was correlated with one dimension of the CERQ: Refocus on planning, ρ(14) = -.70, p < .01. Third, neither VLF; nor HF were significantly linked to trait or state anxiety, all ps < .135, all ps > .20.

Conclusions: Both HF and VLF were linked to cognitive emotion regulation strategies. However, these two measures might be better indicators of this aspect of emotional state.

Keywords: Heart rate variability, Adolescence, psychiatric disorders
disturbances. However, when testing a node-level model predicated on prior clinical findings, a significant correlation was found between adolescent anxiety and left caudate to dorsolateral prefrontal cortex weighted connection strength (r = −.336, p = .045).

**Conclusions:** Present findings establish that structural connectomic differences associated with impaired emotion regulation may be incurred prior to the clinical presentation of anxiety and depression. Future work should endeavor to synthesize present findings with functional modalities in service of furthering a mechanistic understanding of the emergence of mood and anxiety disturbances in adolescence.

**Supported By:** RO1

**Keywords:** connectome, Anxiety, Adolescence, Adolescent Depression, diffusion MRI

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807. Characterizing Similarities and Differences between Preadolescent Girls At-Risk for and Currently Experiencing Anxiety Disorders (ADs)

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**Background:** While anxiety disorders (ADs) frequently have their onset in early childhood, few studies have examined the neural underpinning of childhood ADs. We previously demonstrated that preadolescent children with ADs have increased activation of the amygdala, bed nucleus of the stria terminalis (BNST), and anterior insula (AI) in response to a paradigm that models anticipatory anxiety. Here, we further examine alterations in uncertainty processing in a unique sample of preadolescent girls with a range of symptoms from preclinical, “at-risk” anxiety to clinically-significant ADs.

**Methods:** Forty-eight treatment-naive girls (age 9-11; 36 at-risk, 12 AD), viewed 2-minute blocks of negative or neutral images during an fMRI scan. The emotional pictures were separated by a series of clock images that were either presented in sequential order and “countdown” to image presentation (Certain condition), or were presented in a random order, making the exact timing of picture presentation unknown (Uncertain condition).

**Results:** All subjects demonstrated greater activation during Uncertain blocks, relative to Certain blocks, in the amygdala, BNST, and AI (p < 0.05 corrected), regardless of picture valance. AD girls showed greater activation in the amygdala relative to at-risk girls (p < 0.05), while the magnitude of response in the BNST and AI did not differ between groups.

**Conclusions:** These findings highlight increased amygdala activation early in life that is associated with anticipatory anxiety, a core clinical feature of ADs. The findings also suggest alterations in brain function that are shared between high-risk and AD girls.

**Supported By:** 1R01MH107563

**Keywords:** pediatric anxiety, extended amygdala (CeA/BST), Uncertainty, anticipation, BOLD fMRI

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808. Altered Functional Connectivity between Right Insular Cortex and Default Mode Regions Associated with Perceived Stress and Anxiety during Undergraduate Students’ Finals Week

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University of Wisconsin-Milwaukee

**Background:** The right insular cortex (RIC) has been proposed as an attentional switch, enabling individuals to effectively switch between default mode and attentional control networks. Decreased connectivity between the RIC and default mode regions may thus relate to deficits in switching between these networks, contributing to stress and anxiety levels during stressful periods.

**Methods:** Fifty-seven undergraduate students underwent a resting state functional magnetic imaging scan. Participants’ anxiety and perceived stress were later measured during the week of final exams using the Perceived Stress Scale (PSS) and State-Trait Anxiety Inventory (STAI). Functional connectivity was examined between the RIC and precuneus, posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), and left and right parietal cortices (LLP and RLP). Resulting r-values were correlated with PSS and STAI scores.

**Results:** Results indicated that RIC-precuneus (p = .019) and RIC-PCC (p = .025) connectivity were negatively correlated with PSS scores. RIC-precuneus connectivity was also significantly correlated with state anxiety (p = .017), but not RIC-PCC (p = .084). This pattern was reversed for trait anxiety, with RIC-precuneus connectivity not reaching significance (p = .085), while RIC-PCC connectivity was significantly correlated (p = .023). There were no significant correlations between any of the other pairings (RIC-mPFC/RLP/LLP) and any of the self-report measures (all ps > .05).

**Conclusions:** Decreased functional connectivity RIC-precuneus and RIC-PCC is associated with heightened perceived stress and anxiety. Connectivity with the precuneus may be particularly relevant, given its stronger association with state anxiety. Potentially, this altered connectivity may indicate difficulties with switching out of self-focused attention during times of stress (i.e., final exams), contributing to elevated anxiety and perceived stress.

**Supported By:** NIH K01 MH086809

**Keywords:** insular cortex, Anxiety, Perceived stress, Default Mode Network, resting state functional MRI

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809. Event-Related Functional Spectroscopy of Human Amygdala Implicates Excessive Excitation in Autistic Social Impairment

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**Background:** The hallmark of Autism Spectrum Disorders (ASD) is abnormal reciprocal social behavior, but it remains...
hotly debated whether this represents social oblivion or avoidance due to excessive reactivity. To address this, we developed a novel event-related functional proton magnetic resonance spectroscopy (fMRS) to measure glutamate and GABA dynamics _in-vivo_ in the human amygdala.

**Methods:** We adapted amygdala-specific spectroscopy to target dorsal basal and lateral nuclei and GABAergic centromedial regions. Using a task that previously showed excessive amygdala fMRI activation in ASD, we collected fMRS with 3s frames (1.5s TRs averaged over 2 phase cycles) with jittered onset for effective ITI of 1.5s. Homemade software interfaced with LCModel allowed frame-by-frame phasing and frequency-correction and produced averaged, stimulus-locked time courses with temporal smoothing to characterize evoked neurochemical responses. Behavioral severity indexed by Social Responsiveness Scale, averaged across 2 raters, was available for 7 participants.

**Results:** All 8 participants in our initial ASD sample (age 12-27y) show grossly abnormal glutamate dynamics when viewing emotional faces. The slope and area under the curve of this abnormal deflection predicts overall social impairment ($p = 0.04$) and especially the social motivation domain such that more glutamate is associated with more impairment. Greater evoked GABA (area under the curve) predicts less social impairment, particularly in the domain of social communication ($r = -0.87, p = 0.03$).

**Conclusions:** Abnormal glutamatergic and GABAergic responses to social stimuli may contribute uniquely to behavioral profiles but both implicate excessive excitation/inhibition in the social impairments of ASD. Further study is warranted.

**Supported By:** R01 MH097464; 2015 NARSAD Young Investigator Award

**Keywords:** Proton Magnetic Resonance Spectroscopy, Autism Spectrum Disorder, Amygdala, functional imaging, glutamate or GABA

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810. Adolescents’ Gender and Substance Use Exposure Interact to Predict Depression-Related Amygdala Functional Connectivity during Social Reward

**Gabriela Alarcon, Kristen Eckstrand, Arpita Mohanty, and Erika Forbes**

University of Pittsburgh

**Background:** Amygdala resting state functional connectivity (FC) has been implicated in major depression; however, few studies have examined amygdala task-related FC in relation to depressive symptoms during adolescence. Social reward is one such relevant context given the amygdala’s role in emotion processing, social reward processing alterations in depression and adolescents’ heightened sensitivity to reward and social information. Here, we measured FC during social reward and explored moderating effects of gender and substance use exposure (SUE) due to their associations with depressive symptoms.

**Methods:** Forty-six healthy adolescents completed questionnaires assessing substance use (Youth Risk Behavior Survey) and depressive symptoms (Center for Epidemiologic Studies Depression Scale), and a social reward task during functional magnetic resonance imaging. Depressive symptoms were regressed against whole-brain FC of bilateral amygdalae using the CONN toolbox (voxel and cluster $p<0.0001$, FDR). Post-hoc multivariate ANOVAs assessed the effects of gender and SUE, controlling for age, on FC.

**Results:** Depressive symptoms were positively associated with FC within amygdalae and between amygdala and 1) putamen, 2) insula, 3) temporo-occipital cortex and 4) subgenual cingulate cortex (SCC). A significant interaction between gender and SUE was observed for amygdala-SCC FC, such that boys with no SUE had the strongest FC.

**Conclusions:** Top-down modulation of the amygdala by SCC ordinarily functions to regulate emotional experiences; however, in social reward contexts, this function may be weakened in youth with SUE and in girls, manifesting in fewer depressive symptoms. These findings highlight the importance social context when determining the utility of amygdala FC as a predictor of depressive symptoms.

**Supported By:** R21 DA033612; T32 MH018951

**Keywords:** Adolescence, Depressive symptoms, Substance use, Functional connectivity, Social reward

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811. Is Olanzapine Predicted to Have Antidepressant Effects on Juvenile Rats in the Forced Swim Test?

**Alicia Cho, Erica Stanley, and David Middlemas**

Kirksville College of Osteopathic Medicine

**Background:** Clinical data indicate that there are developmental differences in antidepressant drug action. Children and adolescents respond to Selective Serotonin Reuptake Inhibitors (SSRIs), but not to other classes of antidepressants. Recently atypical antipsychotic drugs, which are 5HT2A receptor antagonists and less potent Dopamine Receptor 2 antagonists, have been approved for adjunctive therapy with SSRIs in adults for treatment resistant depression. Olanzapine is approved for schizophrenia in children, but it is not approved yet for adjunctive therapy for depression in children.

**Methods:** We are testing whether Olanzapine is predicted to be an antidepressant in a juvenile rodent model. Olanzapine was tested in the Forced Swim Test (FST), a behavioral paradigm that predicts antidepressant activity, at 2, 5, and 10 mgkg-1 on Post Natal Day 22 (PND 22) with Sprague Dawley rats.

**Results:** Olanzapine treated PND 22 rats spent more time immobile than the placebo treated rats. Rats treated with a combination of Fluoxetine and Olanzapine at a 1:1 ratio at 2 mgkg-1 spent significantly less time immobile than rats treated with Olanzapine or the placebo.

**Conclusions:** These results indicate Olanzapine alone is not predicted to have an antidepressant effect in adolescents but may have an antidepressant effect when combined with Fluoxetine.

**Supported By:** Department of Pharmacology, KCOM, A.T. Still University
812. Individuals at Risk for Depression Recruit Default-Mode Network to Process Stress-Relevant Information

Cecilia Westbrook, Alena Patsenko, Lyn Abramson, Jeanette Mumford, and Richard Davidson

University of Wisconsin - Madison

**Background:** Negative cognitive style (NCS) comprises a tendency to make stable, global and internal attributions for negative events, and ascribe negative consequences to them. NCS is known to put individuals at greater risk for depression following negative events, but the neural mechanisms are unknown. We sought to assess differences in neural responding to information related to a recent negative event in individuals with and without NCS, in order to elucidate how these individuals differentially process life events.

**Methods:** Undergraduates in a large introductory psychology course were screened for NCS at the beginning of the semester. Following a midterm exam, students who performed worse than their aspirations completed an fMRI task in which they had to remember the order of words. Unbeknownst to participants, a third of the trials contained words from their study materials for the exam (e.g., “neuron”), while a third contained negative but non-self-relevant words (e.g., “cancer”).

**Results:** When deliberating about exam-related (vs. neutral) words, students with NCS had greater activation in R dorsolateral prefrontal cortex and angular gyrus, as well as greater activation in L angular gyrus when deliberating about negative (vs. neutral) words. These activations overlapped with the resting-state default-mode network.

**Conclusions:** Individuals with NCS may process information related to negative events by recruiting DMN brain regions. This suggests they may represent these events in abstract, self-referential ways, consistent with rumination. This is the first study to our knowledge to assess processing of event-specific information in at-risk individuals, and informs our understanding of diathesis-stress interactions in development of depression.

**Supported By:** NIMH R01

**Keywords:** Depression, Default Mode Network, cognitive style, risk for mood disorder, fMRI

813. Altered Genomic Expression in Hippocampal Dentate Gyrus in Depression

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1University of Mississippi Medical Center, 2Case Western Reserve University, 3Cleveland VA Medical Center

**Background:** Major Depressive Disorder (MDD) is a common psychiatric disease and available medications are often not effective. Decreases in hippocampal volume with increasing duration of depression suggest altered gene expression and a decrease in neurogenesis.

**Methods:** Tissue punches from the dentate gyrus were collected from 23 subjects (MDD, medication-free) and 24 normal controls. Total RNA was isolated (Invitrogen PureLink RNA Mini kit) with RNA Quality Index > 6. Whole transcriptome paired-end RNA-sequencing was performed using an Illumina NextSeq 500.

**Results:** After read alignment with GSNAP and annotation using the ‘tuxedo’ pipeline, analyses using ‘cuffdiff’ revealed 32 genes differentially expressed (Lumenogix™, FDR < 0.05). Genes downregulated in MDD included several with inflammatory function (IGS15, IFI44L1, IFI6, NRA1) and GABABR1. Genes upregulated in MDD included those with cytokine function (SOCS3, CCL2), inhibiting angiogenesis (ADM, ADAMTS9), and the KANSL1 gene, a histone acetyltransferase. Gene set analyses revealed unique genes differentially expressed vs. normal controls: 13 in single episode/MDD, and 18 in multiple episode/MDD, 10 (in MDD/suicide) and 24 (in MDD/non-suicide). Ingenuity Pathway Analysis revealed an overrepresentation of genes for 1) single episode MDD in the ERK/MAPK, TNF-R2, and glucocorticoid receptor pathways, 2) multiple episode MDD in the VEGF, eNOS, and IL-8 pathways, and 3) MDD/suicide in the thioredoxin and inflammation-related pathways.

**Conclusions:** Inflammatory and neurogenesis-related (ERK/MAPK & VEGF) signaling pathways appear significantly altered in the hippocampus in MDD, with inflammatory pathways preferentially altered in MDD/suicide vs. MDD/non-suicide. COBRE P30 GM103328.

**Supported By:** NIGMS/NIH COBRE P30 103328

**Keywords:** Hippocampus, Gene Expression, Major Depressive Disorder (MDD), Next generation Sequencing

814. Klotho Dysfunction: A New Piece in Bipolar Disorder's Inflammation Puzzle

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**Background:** Despite of the classic corollary than Bipolar Disorder (BD) is a chronic psychiatric disorder, mounting evidence has appointed BD as a multi-systemic condition. Moreover, BD has been associated with premature and/or accelerated aging process. Klotho is a key regulator of aging and plays a role in para-inflammation. Regarding accelerated aging process and low-grade inflammation in BD, the aim of this study was to evaluate circulating klotho levels among BD patients.

**Methods:** The current study included 40 patients with type 1 BD and 30 controls matched for age, gender, and educational attainment. Psychiatric diagnosis was confirmed by M.I.N.I. International Neuropsychiatric Interview, patients were assessed...
with the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS). Klotho levels were determined by enzyme-linked immunosorbent assay.

**Results:** BD patients presented increased Klotho plasma levels in comparison with controls ($p < 0.005$). In patients, Klotho plasma levels negatively correlated with age ($\rho = -0.38, p = 0.02$), and length of illness ($\rho = -0.43, p = 0.01$), while positively correlated with HDRS scores ($\rho = 0.56, p < 0.001$). ANCOVA analysis confirmed that HDRS scores were independent associated with Klotho levels ($F = 17.753, p < 0.001, \text{adj. } R^2 = 0.862$).

**Conclusions:** This preliminary result suggests that Klotho-related pathway is altered in BD. As Klotho levels independently correlated with age and depressive symptoms, this may suggest that Klotho might play a role in the pathophysiology of mood disorder. Elevated levels of klotho in BD might be a compensatory mechanism associated with the disorder.

**Keywords:** Mania, Bipolar Disorder, Inflammation, Neurobiology, Mood

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**815. Bilateral Repetitive Transcranial Magnetic Stimulation (rTMS) Decreases Suicidality in Adults with Treatment Resistant Depression**

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$^1$University of Toronto and CAMH, $^2$Centre for Addiction and Mental Health, $^3$University of Toronto, $^4$Toronto Western Hospital, $^5$Monash Alfred Psychiatric Research Centre

**Background:** Novel treatments are needed for patients suffering from suicidality. This study was developed in order to evaluate the effects of repetitive transcranical magnetic stimulation (rTMS) on suicidality in patients with treatment resistant major depression (TRD).

**Methods:** We pooled data from two published prospective randomized controlled trials of rTMS applied to the dorsolateral prefrontal cortex (DLPFC) for three to six weeks in patients with TRD. We compared the effect of bilateral, left unilateral, and sham rTMS on suicidality (N=156) as measured by the suicide item of the Hamilton Rating Scale for Depression (HAMD17).

**Results:** Suicidality resolved in 40.4%, 26.8%, and 18.8% of participants randomized to bilateral, left unilateral, and sham rTMS respectively. The difference between bilateral and sham rTMS was significant (OR: 3.03; 95% CI: [1.19-7.71]; $p=0.02$), unlike the difference between left unilateral and sham rTMS (OR:1.59; 95% CI: [0.61-4.12]; $p=0.33$). There was only a modest correlation between change in suicidality and change in depression severity (Pearson $r=0.38; p<0.001$).

**Conclusions:** Bilateral rTMS was superior to sham rTMS in reducing suicidality in patients with TRD. Only a small portion of the reduction in suicidality was attributable to the reduction in depressive symptoms. This suggests that suicidality could be a specific target symptom for rTMS. Additional work is needed to determine whether rTMS is also effective in reducing suicidality in patients with other psychiatric disorders.

**Keywords:** rTMS, Suicide, Treatment Resistant Depression, Endophenotypes, DLPFC

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**816. Striatal Dopamine D2/D3 Receptor Availability Predicts Episodic Verbal Memory and Executive Function in Medication-Free Major Depressive Disorder Patients**

Joseph Kim$^1$, Sara Weisenbach$^2$, Erich Avery$^3$, Joseph Heffernan$^4$, Marta Pecina$^5$, Jon-Kar Zubieta$^2$, and Brian Mickey$^7$

$^1$University of Utah School of Medicine, $^2$University of Utah, $^3$University of Michigan, $^4$University of Wisconsin, $^5$University of Pittsburgh

**Background:** The striatum is known to mediate executive functioning, hedonic responses and behavior. In the present study we explore the association between striatal D2/D3 receptor availability and cognitive function in MDD.

**Methods:** 27 right-handed medication-free participants diagnosed with DSM-IV Major Depressive Disorder (MDD; 18 females, ages 18-59, mean ± SD: 37.3 ± 14.1) performed the Stropp Color-Word Interference Task (Stroop), the Wisconsin Card Sorting Task (WCST), and the California Verbal Learning Test-second edition (CVLT-II). Subsequently, study participants were scanned with positron emission tomography (PET) using $[^{11}C]$raclopride. D2/D3 receptor binding potential (BP) was extracted for three striatal regions bilaterally: caudate, putamen, and nucleus accumbens (NAcc). Partial correlation analyses were conducted using striatal BP data as a predictor, age, sex, and smoking status as covariates, and Stroop, WCST, and CVLT-II performance as outcome variables.

**Results:** Lower D2/D3 receptor availability in the putamen predicted worse cognitive flexibility (WCST overall error, $r=-.53$, $p<.05$; perseverative error, $r=.53$, $p<.01$) as well as greater difficulty with verbal episodic memory learning and recall (learning-slope, $r=.46$, $p<.05$; long-delay-free-recall, $r=.57$, $p<.005$). On the other hand, lower D2/D3 receptor availability in the NAcc predicted greater difficulty with response inhibition (color-word-interference-trial, $r=.43$, $p<.05$) as well as attentional difficulty in the context of verbal memory learning (total learned over 5 trials, $r=.65$, $p<.001$).

**Conclusions:** Lower D2/D3 receptor availability in the putamen and NAcc is associated with poorer executive function and episodic verbal memory in medication-free MDD patients. These results suggest a potential treatment target for MDD patients experiencing decrements in cognitive functioning.

**Supported By:** NIH R01 MH086858 (Dr. Zubieta)

**Keywords:** Dopamine, Nucleus Accumbens, Executive Function, Major Depressive Disorder (MDD), Raclopride

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**817. Neuropeptide Y Genetic Risk Affects Striatal Response to Potential Loss**

Katherine Warthen$^2$, Benjamin Sanford$^3$, Kendal Walker$^3$, Shana Black$^2$, Mike Angstadt$^3$, Chandra Sripath$^3$, Robert Welsh$^2$, Jon-Kar Zubieta$^2$, Margit Burmeister$^3$, and Brian Mickey$^7$

**Background:** Novel treatments are needed for patients suffering from suicidality. This study was developed in order to evaluate the effects of repetitive transcranial magnetic stimulation (rTMS) on suicidality in patients with treatment resistant major depression (TRD).

**Methods:** We pooled data from two published prospective randomized controlled trials of rTMS applied to the dorsolateral prefrontal cortex (DLPFC) for three to six weeks in patients with TRD. We compared the effect of bilateral, left unilateral, and sham rTMS on suicidality (N=156) as measured by the suicide item of the Hamilton Rating Scale for Depression (HAMD17).

**Results:** Suicidality resolved in 40.4%, 26.8%, and 18.8% of participants randomized to bilateral, left unilateral, and sham rTMS respectively. The difference between bilateral and sham rTMS was significant (OR: 3.03; 95% CI: [1.19-7.71]; $p=0.02$), unlike the difference between left unilateral and sham rTMS (OR:1.59; 95% CI: [0.61-4.12]; $p=0.33$). There was only a modest correlation between change in suicidality and change in depression severity (Pearson $r=0.38; p<0.001$).

**Conclusions:** Bilateral rTMS was superior to sham rTMS in reducing suicidality in patients with TRD. Only a small portion of the reduction in suicidality was attributable to the reduction in depressive symptoms. This suggests that suicidality could be a specific target symptom for rTMS. Additional work is needed to determine whether rTMS is also effective in reducing suicidality in patients with other psychiatric disorders.

**Keywords:** rTMS, Suicide, Treatment Resistant Depression, Endophenotypes, DLPFC

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**817. Neuropeptide Y Genetic Risk Affects Striatal Response to Potential Loss**

Katherine Warthen$^2$, Benjamin Sanford$^3$, Kendal Walker$^3$, Shana Black$^2$, Mike Angstadt$^3$, Chandra Sripath$^3$, Robert Welsh$^2$, Jon-Kar Zubieta$^2$, Margit Burmeister$^3$, and Brian Mickey$^7$
818. Halides in Drinking Water are Inversely Correlated with Suicide Rates

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Background: Prior research has identified a positive relationship between hospitalization with infections and risk of suicide. Thus, it is possible that eradicating microbial pathogens can reduce risk of suicide. We evaluated data from public drinking water sources in the US. In order to eliminate infection-causing microorganisms, drinking water is commonly chlorinated. When chlorine is added to water, potentially toxic chemical by-products like trihalomethanes (THM) and haloacetic acids (HAA) form. Fluoride, which is chemically similar to chlorine, is a drinking water additive used to prevent tooth decay and has been found to possess antimicrobial effects.

Methods: To measure the effects of halides on drinking water, state data was gathered from the Environmental Working Group on HAA and THM levels found in tap water reported in 2012. HAA and THM measurements were averaged for each state from the largest water utilities (n=201). To measure effects of fluoridated water, state data of persons receiving fluoridated water was collected from the CDC for years 2010, 2012 and 2014.

Results: Suicide rates were negatively correlated with average state HAA measurements (r = -0.30, p = 0.048) and combined HAA and THM measurements (r = -0.30, p = 0.039). Suicide rates were also negatively correlated with persons exposed to fluoridated water for years 2010, 2012, 2014 (r = -0.386, p = 0.05, r = -0.324, p = 0.020 and r = -0.342, p = 0.014).

Conclusions: These results suggest that water chlorination (reflected in residual levels of HAA and THM) and fluoridation may be correlated with a decrease in the rate of suicide by reducing the levels of microorganisms found in drinking water.

Supported By: USTAR

Keywords: Suicide

819. Right Temporoparietal Junction Response to Social Reward Moderates the Relation between Naturalistic Emotional Closeness and Positive Affect among Adolescents

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Background: Experiencing emotional closeness can be rewarding and is related to lower anhedonic depressive symptoms. Investigating function in brain regions implicated in social cognition—such as right temporoparietal junction (rTPJ)—may help elucidate whether engagement in social-cognitive processing alters the extent to which emotional closeness enhances positive affect.

Methods: Participants were 34 typically-developing adolescents (ages 14-18). As part of a two-week ecological momentary assessment, participants received multiple phone calls per day and reported: whether they were with someone and how close they felt to them; and ratings of their current positive affect and their peak level of happiness over the past hour. Participants also completed a laboratory social reward fMRI task in which they received social feedback from peers represented by standardized faces.

Results: Multilevel modeling was used to examine rTPJ as a moderator in associations between closeness and positive affect. Surprisingly, adolescents with greater rTPJ social reward response exhibited a weaker positive association between closeness and concurrent positive affect than adolescents with lower rTPJ response, t(185) = -2.52, p = .013.
However, adolescents with greater rTPJ response demonstrated a positive association between closeness and peak happiness a few hours later, whereas adolescents with lower rTPJ response did not, t(158) = 2.46, p = .015.

Conclusions: Overall, the findings suggest that although greater engagement in social cognition during rewarding social contexts tempers the short-term mood effects of emotional closeness, it helps sustain affective benefits from emotional closeness over time. Future research may demonstrate that the ability to sustain affective benefits from emotional closeness may help protect against depression.

Supported By: NIH R21 DA033612
Keywords: Social reward, Positive affect, temporo-parietal junction, Neuroimaging, Social

820. Latent Factors of Psychopathology and Grey Matter Volume
Kendra Hinton1, Victoria Villalta-Gil1, Scott Perkins1, Leah Burgess1, Joshua Benton1, Neil Woodward2, Bennett Landman2, Benjamin Lahey3, and David Zald1

Background: Psychiatric disorders are often comorbid, and can be organized into higher order latent factors including internalizing and externalizing as well as a general bifactor to account for overlap across disorders. Studies have implicated the limbic-paralimbic (LP) network in internalizing disorders and the mesocorticolimbic (MCS) network in externalizing disorders [1, 2]. Whether these networks are specific to internalizing and externalizing disorders or broadly related to psychopathology through the general factor remains unclear.

Methods: 444 subjects (233 women, 26.01 ±1.79 y.o.) from the Tennessee Twin Study (TTS) completed a structured clinical interview and a T1 scan [3, 4]. Multi-atlas segmentation was used to produce grey matter volume (divided by total intracranial volume) [5, 6] from bilateral LP (hippocampus, amygdala, and anterior insula) and bilateral MCS (dorsal striatum (DS), and ventral striatum (VS)) and tested for correlations with internalizing and externalizing scores respectively. General factor scores were correlated with all regions.

Results: There were no significant relationships with internalizing scores (ps > .1). Externalizing scores had a significant positive correlation with (ps < .01) right DS (r(442) = .14), left DS (r(442) = .14), left VS (r(442) = .15), and right VS (r(442) = .17). General factor scores had a significant positive correlation with (ps < .01) the left VS (r(442) = .13) and right VS (r(442) = .16).

Conclusions: Findings implicate the MCS in externalizing psychopathology and the VS in the general factor. While the DS may be more specifically related to externalizing psychopathology, the VS may be related more broadly to psychopathology.

Supported By: R01MH098098
Keywords: externalizing, internalizing, general factor, Gray Matter Volume

821. 96 Hour Infusion of Ketamine for Treatment Resistant Depression: Clinical and Resting State Connectivity Findings
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Washington University School of Medicine

Background: Ketamine has shown benefits as a novel antidepressant, but its actions are limited by brief duration of improvement. We propose that a higher-dose, prolonged (96hr) infusion of ketamine is required to reset the NMDA receptor and provide sustained benefits.

Methods: 22 adults with treatment-resistant depression underwent a 96hr infusion of ketamine. Clonidine, and alpha-2 agonist, was co-administered to block psychotomimetic side effects of ketamine. We measured clinical response using the Montgomery Asberg Depression Rating Scale (MADRS) and Clinical Global Impressions-Improvement Scale (CGI-I) for 8 weeks post-infusion. We also examined functional connectivity changes in brain networks using resting-state fMRI before and two weeks after the infusion.

Results: 21/22 participants completed the infusion. MADRS score changed from 28.5 (mean) pre-infusion to 9.2 1 day post-infusion. Effects were largely sustained, with average MADRS score 14.4 at 8 weeks post-infusion. The infusion was generally well-tolerated with minimal cognitive and psychotomimetic side effects. Neuroimaging findings show persistent (2-week) network changes; findings will be presented at the SOBP meeting.

Conclusions: ConclusionsKetamine when given as a prolonged infusion provides both a rapid and in many cases sustained response in treatment-resistant depression. Changes in key resting-state networks correlate with this response.

Supported By: Taylor Family Institute for Innovative Psychiatric Research CTSA grant from NCATS to Washington University
Keywords: Ketamine, treatment-resistant depression, Resting state fMRI

822. Abnormal Resting State Functional Connectivity in Bipolar Disorder with and without Psychosis
Sabin Khadka1, Carol Tamminga2, Matcheri Keshavan3, Brett Clementz4, Elliot Gershon5, and Godfrey D Pearson6

Background: The ventral anterior cingulate cortex (vACC) has been identified as a brain region responsible for modulating emotional behavior and is implicated in the pathophysiology of mood disorders. Limited studies have assessed functional-connectivity between vACC and other brain regions or
compared its connectivity patterns among bipolar patients with and without psychosis.

**Methods:** Resting state functional MR images (rsfMRI, 5 min, eyes open) were collected from 40 bipolar disorder patients with psychosis (BP-P), 47 bipolar disorder patients without psychosis (BP) and 49 healthy controls (HC) as a part of the "Psychosis and Affective Research Domains and Intermediate Phenotypes" study. Standard preprocessing steps for rsfMRI were conducted using the DPARSFA toolbox. For seed-based connectivity analysis, a 5 mm-spherical region-of-interest from vACC (MNI: 2,37,-1) was used. Group comparisons were tested using threshold-free cluster enhancement analysis with 5000 permutations and family-wise error correction (p<0.05).

**Results:** When compared to HC, BP-P showed significantly greater connectivity with vACC in thalamus (R/L), mid-cingulate/sensory-motor area and cuneus and less connectivity in anterior/paracingulate gyrus, precentral gyrus, precuneus/posterior cingulate, medial frontal gyrus(R/L), parahippocampal gyrus (R/L), middle temporal gyrus(L) and caudate(R). Also, when compared to HC, BP showed greater connectivity with vACC in Insula/Inferior frontal gyrus (L), caudate (R), parahippocampus (L), thalamus(R/L) and fronto-polar region (R/L) and less connectivity in cingulate gyrus, superior frontal gyrus (R/L), supplementary motor area, precentral gyrus, insula(R) and middle frontal gyrus (L/R).

**Conclusions:** In this study we investigated functional-connectivity of vACC and how brain connectivity differentiates BP-P and BP when compared to HC. BP-P and BP showed some overlapping but mainly unique brain regions that showed significant connectivity differences with vACC.

**Supported By:** R01MH096913-01A1

**Keywords:** Bipolar, rsfMRI, Brain connectivity, Mood disorder

823. Quantification of Subjective Intraoperative Response to Deep Brain Stimulation of the Subcallosal Cingulate Using Facial Dynamics

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Emory University

**Background:** Severe depression is associated with a state of low variability in facial expressivity and responsiveness. Subcallosal cingulate deep brain stimulation (SCC DBS) is a promising experimental treatment for patients suffering from severe, treatment-resistant depression. Previously, we have shown that a dynamic latent variable model (DLVM) applied to videotaped interviews of SCC DBS subjects can distinguish three phases in the course of recovery from depression (Harati et. al., 2016). Here we investigate whether a DLVM can differentiate between different DBS contacts during intraoperative stimulation, given reports of acute behavioral effects predicting long-term antidepressant response.

**Methods:** A DLVM, applied to video recordings of intraoperative stimulation testing, was used to learn a low dimensional set of dynamic factors to explain observed covariance across high-dimensional pixels within each video frame and across time. Analysis was performed on the weighted average of the transition matrix over all modes. Dynamical properties of the video are characterized by eigenvalues of this weighted state transition matrix, specifically, the slope of eigenvalues attenuation.

**Results:** In five of seven subjects, increased variability of facial expression dynamics was associated with intraoperative stimulation of a contact used for chronic stimulation. All subjects were treatment responders.

**Conclusions:** Quantification of facial expression using dynamic latent variable models may be a promising biomarker of an acute stimulation effect that may guide selection of contacts for chronic DBS. Future directions include analysis of white matter tracts associated with contacts showing increased facial variability, to understand the neural network underlying the relationship between facial expression variability and depression.

**Supported By:** Hope for Depression Research Foundation

**Keywords:** Subcallosal Cingulate, Deep Brain Stimulation, facial expression, dynamic latent variable model

824. Impact of Anxiety on Neural Responses to Incentives

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**Background:** Potential gains and losses motivate behavior and activate reward processing brain regions, including the ventral striatum (VS). Additionally, the delivery of negative events results in increased neural activity within the dorsal anterior cingulate cortex (dACC). Here, we test how neural responses during the anticipation and delivery of monetary incentives are impacted by anxiety.

**Methods:** In an fMRI scanner, healthy adults (N=50) performed the monetary incentive delay (MID) task under alternating blocks of anxiety and safe conditions, where anxiety was instantiated by administration of an unpredictable mild electric shock to the wrist. Blood oxygen level dependent (BOLD) responses during the anticipation of gains and losses, but not during neutral trials. Furthermore, neural responses to monetary losses within the dACC were enhanced during the anxiety condition and reduced during the safe condition.

**Results:** Whole brain analyses revealed that anxiety enhanced BOLD responses within the VS during the anticipation of gains and losses, but not during neutral trials. Furthermore, neural responses to monetary losses within the dACC were enhanced during the anxiety condition and reduced during the safe condition.

**Conclusions:** Increased activity within the ventral striatum during the anxiety condition may reflect the competition between anxious anticipation and incentive processing. Human participants are more sensitive to monetary losses than to gains and the neural processing of loss within the dACC is uniquely impacted by anxiety. Collectively, our results may shed light on clinical symptomatology such as anhedonia and the sensitivity to negative outcomes observed in those suffering from mood and anxiety disorders.
825. Mapping Anticipatory Anhedonia: An fMRI Study
Joanna Szczepanik1, Jessica Reed2, Allison Nugent2, Elizabeth Ballard3, and Carlos Zarate2
1NIH/NIMH, 2Experimental Therapeutics & Pathophysiology Branch, NIMH

Background: Anhedonia is an important symptom of several psychiatric disorders. Research into clinical presentation and neurobiology of this symptom identified components related to motivation, learning, anticipation and experience of pleasure. We hypothesized that evaluating activity pictures for their appetitive value will be related to subjective ratings of anticipatory anhedonia and reflected in activation of reward relevant brain areas.

Methods: 28 healthy subjects evaluated activity pictures for their appetitive value while undergoing fMRI on 3TGE scanner. Reaction time, accuracy measures and BOLD signal were collected. Subjects also filled out Temporal Experience of Pleasure Scale (TEPS), a measure of anticipatory and consummatory anhedonia.

Results: Subjects were faster to rate activity pictures as liked vs disliked (t-test, p<0.001) and the decision time to rate pictures as liked vs disliked correlated with anticipatory anhedonia as measured by TEPS (r=.51, p=0.006). The BOLD signal during subjectively evaluated liked vs disliked activities co-varied with anticipatory anhedonia in left post-central gyrus. The reaction time to liked vs disliked pictures co-varied with the same BOLD contrast in bilateral thalamus, anterior cingulate and caudate, in left postcentral gyrus and bilateral culmen (FWE-corrected p<0.01), suggesting evaluating activities as enjoyable vs disliked engages limbic circuitry as well as frontal areas previously implicated in studies of reward and emotional processing.

Conclusions: The subjective rating of activity stimuli can be used as an experimental measure of anticipatory anhedonia. The task will be evaluated in clinical populations experiencing symptoms of anhedonia.

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Keywords: anhedonia, reward anticipation, fMRI

826. Neural Correlates of Neuroticism in Healthy Young Males
Philip van Eijndhoven, Lizzy Harmsen, Indira Tendolkar, Aart Schene, Guillen Fernandez, and Indira Tendolkar
Donders Institute for Brain, Cognition and Behaviour

Background: Neuroticism is a personality trait that is often accompanied by both a higher risk for and poorer outcome of psychopathology, especially affective disorders. Recent structural imaging studies suggest that behavioural traits of neuroticism may be related to structural changes in the brain.

Methods: To replicate and extend current findings in a large homogenous sample, we investigated structural brain images of 117 young male subjects of 18-30 years old. Data were assessed using FreeSurfer software, controlling for age and intracranial volume. Based on previous literature, we selected thickness of the orbitofrontal cortex (OFC) and volume of the amygdala, cerebellum and total grey matter to predict levels of neuroticism based on the NEO-FFI scores.

Results: Higher neuroticism scores were predicted by thinning of the left OFC and a smaller volume of the right amygdala.

Conclusions: We demonstrate that neuroticism is accompanied by corticolimbic brain changes in a large, homogeneous sample in the absence of a confounding factor of disease.

Keywords: Structural MRI, neuroticism

827. Functional Connectivity of Midbrain/Brainstem Nuclei in Major Depression
Gerd Wagner, Feliberto de la Cruz, Stephanie Köhler, and Karl-Jürgen Bär
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Background: Previous functional MRI studies in the resting state condition demonstrated an abnormally coordinated network functioning between default-mode (DMN), executive-control (ECN) and the salience network (SN) in Major Depression (MDD). As shown in our previous study, the main monoamine-producing nuclei within midbrain and brainstem were functionally integrated within these networks. Therefore, we aimed to investigate the resting-state functional connectivity (RSFC) and network organization of these nuclei in depressed patients and whether patients receiving antidepressant drugs modulating the 5-HT neurotransmission (SSRI) only and modulating both, the 5-HT and NA neurotransmission (SNRI/NaSSA) differ with regard to the RSFC.

Methods: Resting state fMRI data were acquired in 45 patients with MDD and 45 matched healthy participants. Univariate functional connectivity and graph-based analyses were applied to the functional data.

Results: MDD patients showed reduced RSFC from the ventral tegmental area (VTA) to dorsal anterior cingulate cortex (dACC), mediodorsal thalamus, cerebellum and stronger RSFC from the VTA to the left amygdala and left dorsolateral prefrontal cortex (DLPFC). We further detected group differences in the network membership on the midbrain/brainstem and cortical level. Patients treated with SNRI...
showed different RSFC from locus coeruleus to DLPFC compared to patients with SSRI. In the opposite contrast patients treated with SSRI showed stronger RSFC from dorsal raphe to posterior brain regions compared to patients with SNRI.

**Conclusions:** Abnormal functional connectivity of the VTA as a central region of the salience network may result in an over-attrition of the affective salience of internally-oriented processes and may be associated with anhedonia symptoms in MDD.

**Keywords:** Major Depression, Resting state functional connectivity, Midbrain, VTA, salience network

828. Anxiety Disorders with Subthreshold Hypomania: An Understudied Comorbidity Linked With Substance Abuse

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**Background:** DSM 5 marked the advent of a new affective subtype: major depressive disorder with sub-threshold hypomania (MDD with mixed features). The prevalence of MDD with mixed features and its relationship with substance abuse disorder has been expounded. However, the relationship between primary anxiety disorders, sub-threshold hypomania (anxiety with mixed features), and substance abuse has been largely ignored.

**Methods:** The current study is a retrospective analysis of the prevalence of anxiety disorder(s) with mixed features and the relationship between sub-threshold hypomania and substance abuse disorder in a 335 patient population drawn from SUNY Downstate Medical Center and a private clinic.

**Results:** Mixed features were present in 67% of all patients diagnosed with primary anxiety disorder(s) (99/147) and 78% of all MDD patients in our sample (91/116). Patients presenting with anxiety disorder(s) with mixed features had higher rates of substance abuse (25.3%) than patients with unipolar anxiety disorder(s) (8.3%) [Chi sq=6.78; p=.009]. As a group, patients with sub-threshold hypomania and MDD, anxiety disorder(s), or co-morbid MDD and anxiety disorder(s) were more likely to substance abuse (27.1%) than patients with unipolar forms of MDD, anxiety disorder(s), or comorbid MDD/anxiety disorder(s) (10.1%) [Chi sq=9.53; p=.002].

**Conclusions:** The relationship between primary affective disorders (anxiety disorders in particular), mixed features, and substance abuse disorder merits careful clinical consideration. In our population, patients with sub-threshold hypomania were as likely to substance abuse as patients with hypomania. Elucidating the genetic and neural correlates of mixed features could aid the proper diagnosis of this fleeting symptom set.

**Keywords:** Anxiety Disorder, Mania, Mood disorders, Substance abuse, Comorbidity

829. When the Sparks Don't Fly: Transcranial Direct Current Stimulation over Right Prefrontal Cortex Reduces Negative Emotional Responses to Romantic Rejection

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**Background:** Previous studies suggest that the right ventrolateral prefrontal cortex (vlPFC) plays an important role in down-regulating negative emotional responses to social rejection. One group found that applying transcranial direct current stimulation (tDCS), a form of neuromodulation, over the right vlPFC reduced aggression and hurt feelings following social exclusion. Here, we examined the effects of vlPFC tDCS on state rumination, desire for social interaction, and self-esteem during a romantic rejection task.

**Methods:** A preliminary sample of 7 healthy participants (5 male) between ages 18-25 years participated in 1 anodal tDCS (1.5mA, 20min over the right vlPFC) and 1 sham session in counterbalanced double-blinded order. Following stimulation (or sham), participants received feedback that they were not liked by self-selected, highly desired romantic partners and rated their emotional responses on a 0 - 10 scale.

**Results:** Post-rejection rumination decreased on stimulation days (P = .12) compared to sham days. Additionally, post-rejection decreases in self-esteem and desire for social interaction were attenuated by stimulation (Ps = .29 and .14, respectively) vs. sham.

**Conclusions:** These findings suggest that right vlPFC tDCS reduces rumination and buffers negative effects on self-esteem and social motivation following romantic rejection. We are testing additional participants to confirm these findings and will combine our approach with fMRI in order to localize downstream pathways by which the vlPFC regulates emotional responses to rejection. This will further our understanding of emotion regulation during rejection and guide future research on tDCS treatments for disorders characterized by rejection sensitivity such as major depressive disorder.

**Supported By:** Department of Psychiatry Pilot Grant Program, Stony Brook University

**Keywords:** Social Exclusion, transcranial Direct Current Stimulation, lateral prefrontal cortex, Rumination, Self-Esteem

830. Personality Dysfunction in Depression and Individual Differences in Effortful Emotion Regulation

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¹University of Pittsburgh, ²University of Pittsburgh School of Medicine

**Background:** Comorbid personality dysfunction is a replicated predictor of differential response to cognitive therapy (CT) and antidepressant medication treatments for depression, but the mechanisms underlying these effects are unknown. The goal of
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this study was to examine among depressed adults whether specific dimensions of personality dysfunction interfere with neural mechanisms associated with the reappraisal of negative emotional information, a core process involved in CT.

Methods: fMRI data were collected from 26 unmedicated depressed adults. We examined the relationship between two components of trait neuroticism that are independent of symptom severity, emotional vulnerability (EV) and angry hostility (AH), and neural response during an emotion regulation task in which participants viewed negative interpersonal scenes and either attended to or reappraised the content to alter their emotional reactions.

Results: In whole brain analyses, depressed individuals with higher levels of EV displayed increased activity during reappraisal in the posterior cingulate and precuneus (K=959, FWE-corrected p<0.05), and decreased functional connectivity between the right dorsolateral prefrontal cortex and the right amygdala (K=122, FWE-corrected <0.05). These effects controlled for concurrent depression, anxiety, and the other components of neuroticism.

Conclusions: Depressed adults with higher levels of a particular facet of neuroticism (EV, which reflects difficulty coping with emotion experience) demonstrated increased activity during effortful emotion regulation in regions often associated with self-related processing, as well as decreased connectivity between cognitive control regions and the amygdala. These novel findings represent an important step for understanding how dimensions of personality dysfunction may impact mechanisms associated with particular forms of treatment for depression.

Supported By: K23 MH097889

Keywords: fMRI, unipolar depression, Emotion Regulation, neuroticism, reappraisal

831. Rapid Eye Movement (REM) Sleep is Associated with Increased Parasympathetic Tone and Decreased Suicidal Behavior in Posttraumatic Stress Disorder (PTSD)

Madhulika Gupta and Patricia Jarosz
University of Western Ontario

Background: Suicidal behavior [SB] can be a problem in PTSD patients. REM sleep abnormalities are considered to be a core feature and hallmark of PTSD. To our knowledge there are no reported studies of REM sleep and SB in PTSD.

Methods: 37 consecutive PTSD [DSM-5 criteria] patients [35 female, mean±age: 49.03±12.60 years; exclusion criteria regular use of narcotics/recreational drugs; mean±SD PTSD Checklist score 41.8±17.7 at time of study] completed 3-8 nights of home sleep testing [HST] [WatchPAT200, Itamar; 88.6% agreement with level1 polysomnography in detecting sleep stages]. Patients remained on all usual medications and completed a battery of instruments [including Beck Depression Inventory (BDI), Beck Suicide Scale (BSS)]. Mean scores from study nights with ≥4 hours sleep were analyzed.

Results: There was an inverse correlation between the BSS and %REM [Pearson r= −0.51, p=0.010] which remained significant after the effect of BDI was partialled out [partial r= −0.45, p=0.032]. %REM was inversely correlated with REM latency [Pearson r= −0.38, p=0.030] and %Light sleep [stages N1, N2] [Pearson r= −0.91, p<0.0001]. %REM was directly correlated with %Deep [stage N3] sleep [Pearson r= 0.58, p=0.001].

Conclusions: In our PTSD patients %REM sleep was robustly and inversely related to BSS scores [measure of SB which is often related to activation]. This relation was not mediated by underlying depression. %REM was directly related to measures of parasympathetic tone [eg., %Deep sleep]. High %REM and high REM pressure in PTSD may be a positive index of resilience potential and an indication of the body’s attempt to regain autonomic homeostasis.

Keywords: rapid eye movement sleep, PTSD - Posttraumatic Stress Disorder, Suicide, autonomic nervous system, slow wave sleep

832. Timing is Everything: Developmental Differences in the Effect of Chronic Stress on Extinction in Adolescent Rats

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Background: Adolescence has been viewed as a developmental period in which chronic stress has particularly deleterious effects on fear inhibition. However, this premise is largely based on findings that adolescents are more sensitive to chronic stress than adults. If adolescence is indeed a stress-sensitive period, then chronic stress should also have more deleterious effects on fear extinction retention at that stage of development than during an earlier developmental period (i.e., juveniles).

Methods: Chronic stress was modelled by one week’s exposure to the stress hormone Corticosterone (Cort; 200μg/ml in the drinking water of rats. Six days later animals underwent fear conditioning and two extinction training sessions (Experiment 1) or were injected with the NMDA receptor partial agonist D-cycloserine (15 mg/kg; s.c.) or saline after one extinction session (Experiment 2).

Results: In Experiment 1, adolescent rats exposed to Cort during adolescence displayed poor extinction retention compared to controls whereas adolescents exposed to Cort during the juvenile period exhibited good extinction retention (ns=7-12; interaction p=0.011). In Experiment 2, relative to saline-treated adolescents, adolescents injected with D-cycloserine exhibited enhanced extinction retention if they had received Cort during the juvenile period (ns=11-12, p=.042) but not during adolescence (ns= 12-14, p=.754).

Conclusions: The results demonstrate that two manipulations that have been shown to enhance extinction retention in non-stressed adolescent rats do not do so in stressed adolescents if, and only if, that stress also occurred during adolescence. These findings suggest that adolescence is a stress-sensitive period for the effects of chronic stress on fear inhibition.

Supported By: ARC grant DP150104835, and NHMRC grants APP1086855 and APP1054642.

Keywords: Fear Extinction, Adolescence, Chronic Stress
833. Consequences of Altering Prefrontal-Temporal Lobe Connectivity in Young Nonhuman Primates

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Background: The orbitofrontal cortex (OFC) plays a role in the regulation of anxiety via its interactions with subcortical structures. We demonstrated that large aspiration lesions of the primate OFC decreased threat-related behavioral responses and reduced bed nucleus of the stria terminalis (BST) metabolism. To test whether the white matter fibers coursing through the OFC mediate these effects, we performed aspiration lesions of a narrow strip of the posterior OFC to disrupt fibers of passage.

Methods: Young female monkeys (lesion n=10; controls n=10) were tested in behavioral paradigms focused on threat-related responses. MRI and FDG-PET scans were used to assess lesion-induced changes in brain structure and function.

Results: Lesion extent and disruption of the white matter tracts (i.e. uncinate fasciculus) connecting the OFC to temporal lobe structures were confirmed using morphometric analyses and tractography. Responses of the OFC-strap lesion subjects to a potentially threatening novel conspecific were particularly interesting in that lesioned subjects received less aggression (p<.05) and tended to freeze less (p=.07). Replicating earlier findings, strip-lesion subjects had reduced threat-related BST metabolism (p <.005, uncorrected). Additionally, lesioned subjects had decreased brain volume (p<.05, FDR corrected) and metabolism (p<.005, uncorrected) in the medial dorsal thalamus.

Conclusions: Damage to the white matter tracts connecting OFC to temporal lobe regions results in behavioral and brain changes that underlie threat processing. These findings suggest an important developmental role for the OFC in regulating the neural circuits and behaviors relevant to adaptive threat-related responses, as well as in stress-related psychopathology.

Supported By: R01 MH79201 and R01MH60451 to MGC; F32MH093092 to BDS

Keywords: Early Life Stress, social defeat stress, Mouse model, Depression, Anxiety

834. Early Life Maternal Separation Stress Increases Vulnerability to Social Defeat Stress

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Background: Associations between stress and mental illness have been well documented, but the cellular and molecular mechanisms through which potential vulnerability factors confer susceptibility vs. resilience to stress remain largely unknown.

Methods: We employed a combination of behavioral assays, western blotting, and real time PCR to determine the effects of maternal separation stress (MSS) on responses to social defeat stress (SDS) in mice.

Results: Our results demonstrate that MSS leads to increased susceptibility to sociability deficits induced by SDS. In addition, both MSS and SDS led to significant changes in the expression of stress-related genes in the frontal cortex, amygdala and nucleus accumbens. Significant alterations in gene expression were largely brain region- and stressor-specific and included several endogenous opioid genes as well as genes involved in histone methylation and beta-catenin signaling.

Conclusions: Overall, our findings suggest that the well-documented association between early life stress and mental illness may result in part from the effects of early life stress on promoting vulnerability to subsequent stress exposure in adulthood. In addition, our results suggest that early life stress may influence adult stress responses by leading to the dysregulation of epigenetic processes and the beta-catenin and endorphin signaling.

Supported By: R01 MH79201 and R01MH60451 to MGC; F32MH093092 to BDS

Keywords: Early Life Stress, social defeat stress, Mouse model, Depression, Anxiety

835. A High-Fat High-Sugar Diet-Induced Impairment of Fear Inhibition and Place-Recognition Memory in Adolescent Rats

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School of Psychology, UNSW Australia

Background: High-fat high-sugar (HFHS) diets are associated with increased prevalence of anxiety disorders and these disorders often emerge in adolescence. However, little is known about the consequences of HFHS diets during adolescence on fear inhibition. The present experiments investigated the effect of a HFHS diet lasting 10 or 21 days on fear extinction in adolescent (Experiments 1 and 3) and adult (Experiment 2) rats.

Methods: Male rats received HFHS pellets (2 h/day; Specialty Feeds, SF04-025) in addition to a chow diet for 10 or 21 days during adolescence or adulthood. Controls received a chow-only diet. Rats were tested for extinction retention as well as object-recognition and place-recognition memory.

Results: Rats exposed to 21, but not 10, days of a HFHS diet in adolescence had higher levels of freezing during a second extinction session compared to controls (Exp. 1: p = .013, ns=8-17; Exp. 3: p = .025, ns=11-13), indicating impaired extinction retention. There was some evidence that this deficit persisted to test the following day (Exp. 1: p = .068; Exp. 3: p = .018). An equivalent 21 days HFHS diet in adulthood did not induce extinction deficits (F<.1; ns=7-11). In addition, rats given a
HFHS diet for 10 days during late adolescence (p = .019) or 21 days (p = .003) across adolescence exhibited impaired hippocampal-dependent place-recognition memory but equivalent perinatal-dependent object-recognition memory compared to controls (F < 1).

Conclusions: These results indicate that adolescence is a sensitive developmental period for HFHS diet-induced impairments of fear inhibition and place-recognition memory compared to adulthood.

Supported By: ARC grant DP150104835, and NHMRC grants APP1086855 and APP1054642

Keywords: Fear Extinction, Adolescence, diet, place-recognition

836. Fingolimod Reduces Active p21-Activated Kinase Levels in Cerebral Tissue
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Background: p21-activated kinase (PAK), a correlate of dendritic spine morphology, has been shown to be aberrantly activated at synaptic structures in Alzheimer Disease (AD). Prior studies in cardiomyocytes have indicated that fingolimod, an immunomodulator used to treat multiple sclerosis, induces activation of PAK. However, the effect of fingolimod on activated PAK (p-PAK) in neurons, either alone, or in the presence of amyloid-beta (Aβ) is not known.

Methods: Dissociated primary neuronal cultures from E18 Sprague-Dawley rats were treated with fingolimod (10nM, 1μM) and whole cell lysate was collected. Western blot for p-PAK and total PAK was performed. A maximum tolerable dose of fingolimod i.p. 5mg/kg/day over seven days was established in adult wild-type (WT) C57Bl/6J mice (n = 12) and p-PAK levels in cerebral cortex were similarly assessed. Finally, 12-month old APPSWE/PSEN1dE9 mice (n = 20) and WT mice (n = 20) were treated with this dose/duration. During fingolimod treatment, mice underwent behavioral testing prior to sacrifice and determination of cortical p-PAK levels.

Results: Fingolimod significantly decreased p-PAK in neuronal culture [mean (S.E.): vehicle = 0.228 (0.16), 10nM = 0.289 (0.16), 1μM = -0.394 (0.16); p = 0.011]. Fingolimod 5mg/kg/day i.p. for 7 days induced a nonsignificant reduction in p-PAK in WT mice [vehicle = 2.22 (0.25), fingolimod = 1.85 (0.15); p = .119]. Fingolimod administration to APPSWE/PSEN1dE9 is ongoing. Results of its effects on p-PAK and behavior will be presented.

Conclusions: Fingolimod appears to decrease p-PAK in cerebral cortex. Confirmation of this effect in the context of Aβ overexpression is warranted, as it may be associated with improved synaptic function, and may inform development of therapeutic targets in AD.

Supported By: R01

Keywords: Alzheimer’s Disease, Dendritic spines, NEURONS CELL CULTURE, Beta-amyloid, Animal Behavior

837. Perinatal Omega-3 Fatty Acid Deficiency is Associated with Hyperactivity in Adolescent Rats: Effects of Psychostimulant and Omega-3 Fatty Acid Treatment
Ruth Asch1, Jennifer Schurdak2, and Robert McNamara2

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Background: Deficient cortical docosahexaenoic acid (DHA) accrual during development may contribute to neuropathological processes associated with ADHD. Specifically, reduced neonatal cortical DHA accrual increases risk for developing ADHD and is associated with persistent perturbations of cortical network connectivity in adolescents. This study investigated the consequences of perinatal DHA deficiency on motor activity in adolescent rats, and investigated potential corrective effects of chronic psychostimulant exposure and/or DHA supplementation.

Methods: Female Long-Evans rats were maintained on omega-3 deficient (DEF) or control (CON) diets starting one month prior to mating. On P21, male pups born to CON dams were weaned onto CON diet (CON). Pups born to DEF dams either remained on the DEF diet or were switched to fish oil (FO)-fortified diet containing DHA. Beginning on P40, one-half of each diet group was treated with amphetamine (1mg/kg) or saline for a total of 30 injections. A final amphetamine challenge (1mg/kg) was conducted 1 week after the last injection. Locomotor activity was collected over the course of the study.

Results: Relative to CON rats, DEF rats had reduced activity in response to the initial placement in the activity chamber. However, on subsequent days DEF rats were hyperactive following placement in the activity chamber. This hyperactivity was not attenuated by chronic amphetamine and/or FO treatment. There were no group differences in response to the amphetamine challenge.

Conclusions: These data suggest that perinatal deficits in cortical DHA accrual produce a hyperactive phenotype in adolescent rats which is not corrected by psychostimulants and/or DHA supplementation.

Supported By: NIH/NIMH R01 MH107378

Keywords: Omega-3 fatty acids, ADHD, Animal Model

838. Network Activity in a Conditional TSC1 Knockout Animal
Brian Theyel1 and Barry Connors2

1Brown University, 2PI

Background: Research in mice with genes known to be highly penetrant for Autism Spectrum Disorder (ASD) in humans is progressing, but the individual neurocircuit abnormalities that cause ASD remain unknown. Here, we present preliminary data from a mouse in which one such gene, TSC1, is deleted in thalamus. This mouse repetitively grooms and seizes, which are both prevalent in the human disease tuberous sclerosis and in individuals with ASD. Emerging data suggest that an imbalance in the ratio of excitation to inhibition in cortex may account for many...
results: 2.75% while saturated fat increased from 2.4 to 25%.

polyunsaturated fat in the Western Diet decreased from 8 to calories; saturated fat was 20% of the total fat intake. Relative with 60% saturated fat. Standard chow was 13% of total

fed a "Western Diet" enriched in total fat (45% of total calories) during seemingly unrelated investigations of cardiac health.

COXIV. Serendipity has provided another rodent model mitochondrial mutations, namely polymerase gamma and

S340

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Supported By: Simons Foundation
Keywords: Autism, Electrophysiology, Animal Model, Networks, Thalamocortical circuitry

839. A High Saturated Fat Diet Produces Mania in Female Rodents
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Background: Background: A bipolar disorder subtype responds to lithium, a glycogen synthase kinase inhibitor. This profile also appears in rodent disease models with mitochondrial mutations, namely polymerase gamma and COXIV. Serendipity has provided another rodent model during seemingly unrelated investigations of cardiac health.

Methods: Methods: 10 male and 10 female FVB mice were fed a "Western Diet" enriched in total fat (45% of total calories) with 60% saturated fat. Standard chow was 13% of total calories; saturated fat was 20% of the total fat intake. Relative to standard chow the proportion of calories from polyunsaturated fat in the Western Diet decreased from 8 to 2.75% while saturated fat increased from 2.4 to 25%.

Results: Results: The female cohort initially had mild weight gain of 5% at 2 weeks which subsequently began to decrease at 4 weeks. At 5 weeks, 8 of 10 mice were at or below baseline weight. Females were sacrificed at week 6 given weight loss from constant hyperkinesis. The behaviorally normal male cohort exhibited relative weight gain and elevated serum free fatty acids. Cardiac muscle analysis revealed significantly lower levels of C18:2 linoleic acid in the fatty acid, diacylglycerol, and triacylglycerol pools. Arachidonic acid levels were unchanged.

Conclusions: Conclusions: Dependent variable amplitude (hyperkinesis) and independent variable ease of manipulation (dietary composition) suggests utility for both testing causal disease models as well as for high throughput screening of possible treatments. This rodent data supports human studies showing disturbed linoleic acid metabolism in bipolar patients.

Supported By: Scientist Development Grant: American Heart Association
Keywords: Bipolar Disorder, Lithium, Mitochondria, linoleic acid, Hyperactivity

840. Developing a Rodent Model of Depression and Neurodegenerative Disease by Targeting ACMSD, a Key Enzyme in the Kynurenine Pathway

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Van Andel Research Institute

Background: 2-Amino 3-carboxymuconate 6-semialdehyde decarboxylase (ACMSD) is a key enzyme responsible for maintaining the balance between the excitotoxin, quinolinic acid (QUIN) and the neuroprotective, picolinic acid (PIC). The balance between the two metabolites might be critical for the vulnerability to develop depressive and neurodegenerative disease. Using crspsr/cas9 technique, we genetically deleted the acmsd gene in order to study the effect of these neuroactive metabolites on neuroinflammation, neurodegeneration and behavior.

Methods: Cas9mRNA and guideRNA's targeting the acmsd gene were injected into fertilized eggs and implanted into a pseudopregnant mice. Founders were genotyped and mutants confirmed using T7E1 endonuclease and sanger sequencing. Using gas chromatography-mass spectrometry (GC-MS), we assessed QUIN and PIC in kidney, liver, brain and plasma. Western blot and RT-PCR was used to confirm acmsd deletion and quantify expression of other enzymes in the pathway.

Results: 18 mice were positive for acmsd deletion (acmsd-/-). 4 mutants were chosen and backcrossed to C57/BL6N. Neither mRNA nor protein expression was observed in 2 of the 4 lines. QUIN was elevated 20-50 fold in liver, kidney, brain and plasma of acmsd-/- compared to wild-type littermates. No changes in the mRNA levels of quinolinate phosphoribosyl transferase (qprt) and kynurenine mono oxygenase (kmo), were observed in the mutants.

Conclusions: ACMSD is critical for maintaining balance between QUIN and PIC, which has profound effects on excitotoxic and inflammatory milieu of the central nervous system. Understanding how this enzyme impacts glutamate neurotransmission, neuroinflammation and subsequently mood and behavior, may lead to the development of novel therapeutics for depression and neurodegenerative disease.

Keywords: crspsr/cas9, ACMSD deletion, kynurenine pathway, Quinolinic acid, Picolinic acid, depression, neurodegenerative disease

841. The Ability of Stress during Adolescence or adulthood to Produce Schizophrenia-Like Pathophysiology is Dependent on the State of the Critical Period

Felipe Gomes, Xiaoting Zhu, and Anthony Grace

University of Pittsburgh

Background: Unregulated stress exposure occurring during the sensitive period of development leads to the emergence of circuit deficits consistent with schizophrenia in the adult. If
accurate, one would predict that re-opening the sensitive period in the adult could make it susceptible to a similar disruption.

**Methods:** Male rats were submitted to a combination of footshock (FS) and restraint stress (RS) during adolescence (PD31–40) or adulthood (PD65–74). The activity of dopamine (DA) neurons in the ventral segmental area (VTA) and the pyramidal in the ventral hippocampus (vHipp) were evaluated 1-2 or 5-6 weeks post-stress. We also evaluate if the administration of valproic acid (VPA; 300 mg/kg), which is known to re-instate the critical period in adults, would recreate an adolescent phenotype of susceptibility to stress.

**Results:** The adolescent stress increased VTA DA population activity 1-2 and 5-6 weeks post-stress, these changes seem to be driven by an increased vHipp activity. FS+RS in adult rats decreased DA population activity 1-2 weeks post-stress, but not after 5-6 weeks. Interestingly, VPA treatment altered the impact of adult stress. When rats were treated with VPA, FS+RS increased VTA DA population activity, similar to that observed with adolescent stress.

**Conclusions:** Timing of the stress is a critical determinant of the pathophysiology that is present in the adult. While adolescent stress could lead to changes that recapitulates the MAM model of schizophrenia, adult stress induced changes observed in animal models of depression. Re-opening the sensitive period in the adult restores vulnerability to stress-induced pathology resembling schizophrenia.

**Supported By:** MH57440

**Keywords:** Adolescence, Stress, Schizophrenia, Dopamine

842. Changes in Hippocampal Subfield Activity Contribute to Psychosis-Like Behaviors in Mice

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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 the severity of psychosis. However, a causal link between this hippocampal dysfunction and psychosis has yet to be determined. Therefore, we sought a mouse preparation where we could manipulate subfield activity independently, selectively, and dynamically.

**Methods:** We infused male C57BL/6J mice (n=5-10/group) with AAVs containing DREADDs to specifically activate or inhibit CA3 or DG, respectively, allowing manipulation of activity acutely with spatial, temporal, and cell-type specificity. Following surgery, we treated mice with vehicle or clozapine-N-oxide, and performed behavioral analysis, utilizing two paradigms associated with a psychosis-like phenotype in mice: prepulse inhibition and fear conditioning. Significance was set at p<0.05.

**Results:** Activation of the ventral (posterior), but not dorsal (anterior) CA3 is sufficient to impair prepulse inhibition. Also, inhibition of the anterior DG can potentiate fear conditioning. Interestingly, this combination of phenotypes resembles those in a reverse translational mouse model of schizophrenic psychosis, where GluN1 is knocked out within DG, inducing homeostatic upregulation of cellular excitability within CA3.

**Conclusions:** Results suggest that different aspects of this psychosis-like phenotype are affected by acute activity within the different hippocampal subfields, possibly modeling the psychosis process and suggesting novel therapeutic targets based upon symptomatology.

**Supported By:** NIMH; NARSAD

**Keywords:** psychosis phenotype, DREADDs, Hippocampal subfields, Animal Behavior, Animal Model

843. Serum Metabolites as a Predictor of Antidepressant Responsiveness in the Co-Med Trial

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1The University of Texas Southwestern Medical Center, 2Baylor College of Medicine

**Background:** The relationship between antidepressant response and fatty acids is unclear. Meta-analysis of 14 studies comparing the total n-3 polyunsaturated fatty acids levels from serum, plasma or erythrocytes in depressed vs non-depressed individuals demonstrates a significantly lower amount of n-3 PUFA in depressed populations. Recent metabolomic studies have also demonstrated decreased concentrations of saturated fatty acids in depressed subjects following antidepressant treatment with sertraline. At this time however, there is no clinical data on whether antidepressants alter fatty acids, and if this effect is related to drug efficacy.

**Methods:** Patient plasma from the CO-MED trial was collected pre- and post- antidepressant treatment. This plasma was then examined using the the Biocartes P180 metabolomic kit. For analysis, metabolite data have been combined with demographic data and study exit QIDS score. We used an elastic net regression method to develop a model of multiple metabolites to predict QIDS.

**Results:** Our initial analysis consisted of a series of individual paired t-tests that did not reveal a significant number of metabolites, or sums of metabolites beyond the expected false positive incidence. Therefore we used an elastic net approach to investigate the relationship between various metabolites. Retained in this model include several novel lipid metabolite biomarkers. Of particular note, baseline and changes in sphingomyelin-OH 22:1 concentration were both predictive of QIDS.

**Conclusions:** Baseline or changes in PUFA concentrations were not predictive of antidepressant responsiveness in the CO-MED trial. Several novel lipids were identified as contributing predictors of responsiveness, including sphingomyelin-OH 22:1.

**Supported By:** R25MH101078
Keywords: Pharmacometabolomics, Depression, Antidepressant response, Biomarkers, lipids

844. Association of microRNA-21 with Oligodendrocyte Alterations in the White Matter in Depression

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University of Mississippi Medical Center

Background: Micro-RNAs inhibit the expression of certain proteins by interfering with mRNA translation. Our previous research has shown that micro-RNA 21 (miR-21) is particularly enriched in mice oligodendrocytes. In addition, we found a reduction in miR-21 in the white matter (WM) underlying the orbitofrontal cortex (OFC) of human subjects with major depressive disorder (MDD) as compared to non-psychiatric controls. Reduction of miR-21 could be associated with alterations in markers of oligodendrocytes, myelin or oligodendrocyte precursors in miR-21 KO mice and in MDD subjects.

Methods: Brains from mice with the gene for miR-21 knocked out (KO) were compared to wild type littermates (wt). Brain tissue sections from KO and wt mice were immunolabeled for platelet-derived growth factor receptor-alpha (PDGFR), a marker of oligodendrocyte precursors, or for myelin basic protein (MBP), a major myelin component. Furthermore, mRNA levels of oligodendrocyte markers in OFC WM were measured by qRT-PCR in MDD and control subjects.

Results: There was greater density of PDGFR-expressing cells in the in the corpus callosum, but reduced area fraction of MBP-immunoreactive fibers in the anterior cingulate cortex of KO mice. In addition, qRT-PCR determinations revealed significant reduction of mRNAs for several oligodendrocyte and myelin proteins in the OFC WM in MDD and correlation to miR-21 levels.

Conclusions: These data suggest that reduction of miR-21 in MDD may alter maturation of oligodendrocyte precursors, which in turn may result in subsequent reduction in the expression of MBP and other myelin-related proteins or in the extent of myelinated fibers in the prefrontal cortex.

Supported By: NIMH grant MH82297, Imaging Core of NIGMS grant P30GM103328 and American Heart Association Grant 12SDG8980032, INBRE.

Keywords: Major Depression, oligodendrocytes, miRNAs, white matter, Myelin

845. Disruption of the Axonal Trafficking of Tyrosine Hydroxylase mRNA Impairs Catecholamine Biosynthesis in the Axons of Sympathetic Neurons

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Background: Tyrosine hydroxylase (TH) is the enzyme that catalyzes the rate-limiting step in the biosynthesis of the catecholamine neurotransmitters. Previously, we identified a 50bp sequence element in the 3’ untranslated region (3’UTR) of TH mRNA that directs TH mRNA localization to distal axons. In the present study, the hypothesis was tested that local translation of TH plays a key role in the biosynthesis of the catecholamine neurotransmitters in the axon and/or presynaptic nerve terminal.

Methods: Using the lentiviral delivery of the CRISPR/Cas9 system, a targeted deletion of the axonal transport sequence element in TH mRNA was developed. In situ hybridization was employed to examine the presence of TH mRNA in the distal axons of CRISPR-treated and control rat superior cervical ganglion (SCG) neurons. Immunocytochemistry was used to examine the level of TH protein, dopamine and norepinephrine in SCG neurons.

Results: Deletion of the axonal transport element reduced the levels of TH mRNA in the distal axons and also reduced the axonal proteins levels of TH and TH phosphorylation at S540 in SCG neurons, as well as diminished the axonal levels and release of dopamine and norepinephrine. Conversely, the local translation of exogenous TH mRNA in the distal axon markedly enhanced TH and NE levels.

Conclusions: Our results provide evidence that TH mRNA trafficking and local synthesis of TH plays an important role in the synthesis of catecholamines, allowing for a rapid response to alterations in the need for neurotransmitter synthesis and release.

Supported By: Division of Intramural Research Programs of the National Institute of Mental Health (Z01MH002768) and by the Division of Intramural Research Programs of the National Human Genome Research Institute.

Keywords: Dopamine, Norepinephrine, axon, CRISPR, mRNA trafficking

846. Human-Derived Astrocytes from Schizophrenia Patients Express Lower Levels of GFAP and S100B

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Background: Schizophrenia (SZ) is a debilitating psychiatric disorder with a worldwide prevalence of 1%; there is a strong genetic component, with an estimated heritability of 70-85%. Glial cells mediate crucial functions in the CNS and alterations in the function of these cells may be an underlying mechanism for SZ development. Here we use astrocytes derived from induced pluripotent stem cells (iPSCs) from subjects from the population isolates of the Central Valley of Costa Rica (CVCR) to explore a role for astrocytes in SZ pathogenesis.

Methods: Lymphoblastoid cells lines (LCLs) from 4 healthy controls (HC) and 5 unrelated SZ patients from the CVCR were transformed into iPSCs using the Epi5™ Episomal iPSC
Reprogramming Kit (Thermo). Neuronal Precursors Cells (NPC) were generated using the AggreWell™ methodology (StemCell Technology) and cultured approximately 45 days in N2B27 medium complemented with 5ng CTNF, 10ng BMP4 and 10ng FGF2 for differentiation into astrocytes. Cells were then stained for GFAP and S100B and the results were analyzed using LAS AF software (Leica).

**Results:** SZ astrocytes expressed lower levels of GFAP (p=0.002) and S100B (p=0.01). These results indicate a possible dysfunction in these cells, such as alterations in the differentiation process.

**Conclusions:** These results suggest that astrocytes can play an important role in the pathogenesis and possible treatment of SZ.

**Supported By:** The University of Texas BRAIN Initiative

**Keywords:** hiPSC, Schizophrenia, Astrocytes

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**847. Hippocampal Neurogenesis in Primates and Its Relations to in vivo and Postmortem Measures of Hippocampal Volume**

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**Background:** Deficits in hippocampal neurogenesis and alterations in hippocampal volume are associated with depression and other stress-related psychopathology. Here, we used bromodeoxyuridine (BrDU) labeling and postmortem histology in conjunction with deformation-based morphometry (DBM) to understand how in vivo and ex vivo measurements of hippocampal volume relate to primate neurogenesis.

**Methods:** Structural MRI images were transformed to standard space, providing DBM data on the volumetric change needed to match the template. Subjects were ten monkeys (5 experimental, 5 control) that were part of a study examining the effects of amygdala corticotropin-releasing factor (CRF) overexpression on anxiety. Animals were injected once daily with BrDU (100 mg/kg, IV) for 5 consecutive days. Thirty days after the last injection tissue was processed for postmortem analyses examining the relations between the number of BrDU-positive cells and both DBM and histological measures of hippocampal volume.

**Results:** The number of BrdU-positive cells was significantly positively correlated with hippocampal volume assessed by postmortem histology (r=0.93; p=0.001) and by MRI (r=0.84; p<0.01). Importantly, hippocampal volume assessed in postmortem tissue was highly correlated with MRI measures of hippocampal volume (r=0.74, p<0.05). All correlations controlled for age and group. Neither measure of hippocampal volume nor BrDU cell number was affected by CRF overexpression.

**Conclusions:** These findings in primates suggest a strong relationship between individual differences in hippocampal neurogenesis and measures of hippocampal volume. Future studies examining the extent to which neurogenesis is causally related to hippocampal volume will be important in interpreting in vivo hippocampal imaging data.

**Supported By:** R01 MH046729

**Keywords:** Anxiety, synaptic plasticity, Structural magnetic resonance imaging, Psychological stress, Rhesus Monkey

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**848. Characterizing Extended Amygdala Neuron Populations in Primates as a Basis for Exploring Altered Ce and BST Function in Anxiety**

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**Background:** Anxiety disorders are linked to alterations in extended amygdala (EA) function. Two nodes of the EA, the central nucleus (Ce) and the bed nucleus of the stria terminalis (BST) are primarily composed of small, striatal-like, GABAergic, neuropeptide-expressing neurons. Importantly, the rodent lateral Ce (CeL) has an uneven anterior-posterior (A-P) distribution of some neuropeptide–expressing populations. While similar, the molecular differences between primate EA and striatum have not been fully investigated and in primates little is known about their A-P distribution. Here, we identify enriched genes in the primate EA compared to striatum and describe the A-P distribution of select neuropeptides.

**Methods:** Human data from the Allen Brain Atlas was validated in monkeys using RNA Sequencing (RNA-Seq). In situ hybridization was used to assess the A-P distribution of differentially expressed genes further analyzed with a linear-mixed effects model.

**Results:** Microarray and RNA-Seq analyses identified somatostatin (SST) and cholecystokinin (CCK) as enriched in the Ce compared to striatum. A significant interaction was found for SST mRNA (F1,12,2=9.5,p=0.009); higher levels of SST were found in the posterior compared to the anterior CeL (F1,4.9=10.14,p=0.02) but not the lateral BST. CCK mRNA distribution was not significantly associated with A-P position in either CeL or BST.

**Conclusions:** These experiments utilize gene data to detect differentially expressed mRNAs between Ce and striatum as a stepping-stone to identifying differences in the A-P expression of neuropeptides within the primate EA. These data will help direct cellular and molecular studies aimed at understanding neuropeptide function and guide target-specific novel therapeutics.

**Supported By:** R01 MH081884; P50 MH100031

**Keywords:** Central Nucleus of the Amygdala, Bed nucleus of the stria terminalis, Non Human Primate, Anxiety Disorder, Gene Expression
849. Glucagon like Peptide 1 as a Predictor of Telomere Length in Non Human Primate Exposed to Early Life Stress
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Background: ELs in nonhuman primates [in the form of maternal variable foraging demand (VFD)] leads to persistent plasma elevations in glucagon-like peptide 1 (GLP-1). GLP-1 is a neurotrophic and neuroprotective factor, which predicts adult neurogenesis in nonhuman primates exposed to VFD compared to controls. Telomeres are an ELS-associated biomarker of aging and cellular stress. While GLP-1 reduces cellular oxidative stress, no studies have examined telomere length in the VFD paradigm as related to GLP-1. We hypothesized that VFD would impact telomere length and be related to GLP-1.

Methods: Leukocyte telomere length was measured in 24 VFD (12 male, 12 female) and 30 control (9 male, 21 female) adult bonnet macaques. qPCR for telomere length was adapted to macaques. Sex, weight, and age were used as covariates; adolescent fasting plasma GLP-1 was related to telomere length.

Results: VFD significantly increased telomere length compared with the non-VFD group [F(1, 48)=9.24, p=.004] when controlling for sex, group by sex, age and weight (one outlier excluded). VFD males [mean(SE)=8.88(0.12)] exhibited increased (p<.05) telomere length versus non-VFD males [mean(SE)=8.35(0.14)]. Female VFD [mean(SE)=9.54(0.12)] showed increased (p<.05) telomere length versus non-VFD females [mean(SE)=9.31(0.09)]. Adolescent GLP-1 was positively associated with adult telomere length in males subjects (r=0.66, p=.003).

Conclusions: The VFD paradigm is a finite ELS exposure, unlike human ELS, which may impact the observed telomere effects. A compensatory increase in GLP-1 may play a role in prolonging telomere length in males. These data suggest studies examining ELS, aging, and cellular stress may reveal both deleterious and resilience-associated factors.

Supported By: NIMH Grant R01MH59990A (JDC)

Keywords: Early Life Stress, Telomere Length, Glucagon like Peptide 1, Resilience, Non Human Primate

850. Identification of Biotypes in Psychosis using Biomarkers and iPSCs
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Background: Disease heterogeneity in psychotic illness presents a challenge. The BSNIP consortium hypothesized that measures of cognition and brain neural activity will identify subgroups of psychosis and represent differences in underlying psychosis pathophysiology. Subsequently, we hypothesized that neurons differentiated from patient-derived induced pluripotent stem cells (iPSCs) may uncover synaptic mechanisms in these novel subgroups.

Methods: A panel of cognitive, neuropsychological and neuroimaging measures were collected for individuals with psychosis (SZ, SAD, BDP) (N=711), relatives (N=883), and healthy comparison subjects (N=278). A subset of individuals provided dermal biopsies for an additional study, which were cultured to establish patient-derived fibroblast lines. Fibroblasts representing all three biotypes and healthy comparisons (N=8) were reprogrammed into iPSCs, validated, and differentiated into neural progenitor cells and cortical-like neurons for molecular and functional assessment.

Results: Analysis of composite measures of cognitive control and sensorimotor reactivity elucidate three distinct psychosis biotypes that do not conform to traditional psychiatric diagnoses. Biotypes demonstrate marked differences in cognition and neurophysiology: Biotype-1/B-1, showing significant cognitive impairment and neural hypoactivity, Biotype-2/B-2, showing moderate cognitive impairment and neural hyperactivity, and Biotype-3/B-3, being most similar to healthy participants. Contrasting synaptic activity in mature neurons from iPSC cells will consistently show hypoactivity in B-1, hyperactivity in B-2, and normal synaptic activity in B-3, using molecular and electrophysiological outcomes.

Keywords: iPSC, psychosis, biomarkers

851. DNA Methylation Evidence against the Accelerated Aging Hypothesis of Schizophrenia
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Background: The accelerated aging hypothesis of SZ posits that physiological changes throughout the body that are associated with normal aging (e.g., insulin resistance, hyperlipidemia, skin thinning, dendritic spine loss, cerebral cortical atrophy, cognitive decline) occur at an earlier age in individuals with SZ than in the general population. Research on this hypothesis has been limited by challenges measuring the biological age of tissues, however, a method to do this using DNA methylation (DNAm) levels at 353 genomic sites was recently described (i.e., the Horvath Method). Here, we use this method to test the hypothesis in postmortem brains from SZ subjects.

Methods: DNA was extracted from superior temporal gyrus (STG) gray matter harvested from 22 SZ subjects and 22 nonpsychiatric control (NPC) subjects. DNAm was measured using the Illumina HumanMethylation450 Array. DNAm age was calculated using the Horvath Method, and DNAm age was calculated.
regressed onto chronological age in NPC subjects. Age acceleration for each subject was calculated as the corresponding residual resulting from the regression.

**Results:** DNAm age correlated with chronological age (NPC, \( r=0.95 \); SZ, \( r=0.96 \)). Age acceleration did not differ between NPC and SZ groups (\( t=1.27, p=0.21 \)).

**Conclusions:** Age acceleration in the STG of SZ subjects was not detected despite prior demonstrations of age-accelerated phenotypes (i.e., dendritic spine loss & cerebral cortical atrophy) in this brain region. The findings argue against accelerated aging of the brain in SZ, and are more in line with hypotheses that the brain changes in SZ are a consequence of aberrant neurodevelopment.

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**Keywords:** DNA methylation, Aging, Human Postmortem Brain, Schizophrenia

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**852. Potential Role of Amygdaloid Histone DNA Methylation Mechanisms in Anxiety and Alcohol Drinking Behaviors**

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**Background:** Anxiety disorders co-morbid with alcoholism play a role in promoting and maintaining alcohol abuse. Here we investigated epigenetic contribution to innate predisposition to alcoholism and anxiety using a genetic animal model of alcoholism with comorbid anxiety.

**Methods:** We used adult male alcohol preferring (P) and non-prefering (NP) rats selectively bred for higher and lower alcohol preference, respectively. Immunolabeling and either in situ or qPCR were used to measure protein and mRNA levels, respectively. Chromatin immunoprecipitation assays determined chromatin H3K9me2 and G9a occupancy, and Methylminer was used to determine DNA methylation levels.

**Results:** The protein and mRNA levels of histone methyltransferase G9a and associated H3K9me2 protein levels were significantly elevated (\( n=4-6; p<.05-.001 \)) in the central and medial nucleus of amygdala (CeA and MeA) of P rats as compared with NP rats. The POMC, MC4r, and Grin2a mRNA levels were also higher (\( n=4-6; p<.01 \)) in P rats, and the repressive G9a and H3K9me2 occupancies were lower (\( n=5-6; p<.05-.01 \)) at their promoters as compared to NP rats. In contrast, Grin2b mRNA expression was lower. G9a occupancy was higher (\( n=5-6; p<.05 \)) without a change in H3K9me2 occupancy at the same promoter site. However, repressive DNA methylation was higher (\( n=6-9; p<.05-.01 \)) at the Grin2b, NPY, and Bdnf exon IV promoters, possibly due to higher (\( n=4-6; p<.05-.001 \)) DNMT3b expression and DNMT activity as compared to NP rats.

**Conclusions:** These data suggest that amygdaloid epigenetic methylation may modify the transcription of several genes pivotal to innate anxiety-like and alcohol-drinking behaviors.

**Supported By:** RO1 AA010005, U01AA019971 and P50AA022538 grants from NIH-NIAAA and VA Senior career scientist and merit award to SCP.

**Keywords:** Alcoholism, Anxiety, Histone Methylation, DNA methylation

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**853. Effect of a Novel NMDA Receptor Modulator, Rapastinel (formerly GLYX-13) in OCD: Proof-Of-Concept**

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**Background:** A single intravenous dose of ketamine produces robust and rapid anti-obessional effects in obsessive-compulsive disorder (OCD), but ketamine’s side effects may limit clinical use. Rapastinel (formerly GLYX-13), an NMDAR modulator, has shown rapid anti-depressant activity without ketamine-like side effects, and may be a new therapeutic strategy for OCD. We conducted the first test of the tolerability and potential efficacy of rapastinel administration in OCD.

**Methods:** Seven unmedicated OCD outpatients (aged 18-55) with at least moderate symptoms received a single 3-5 minute IV push of rapastinel (dose = 10 mg/kg). At baseline, 90, and 230 minutes post-infusion, patients self-rated the severity of their obsessions and compulsions (YBOCS scale), anxiety (BAI), and depression (BDI). At baseline and one week post-infusion, an independent evaluator assessed OCD severity using the Y-BOCS, and patients self-rated anxiety (BAI) and depression (BDI). Outcomes were analyzed using a non-parametric Wilcoxon signed-rank matched-pairs test (\( \alpha = .05 \), two-tailed).

**Results:** Compared to baseline, YBOCS, BAI, and BDI scores were significantly lower at 90 and 230 minutes post-infusion (all \( p \) values <.05). Y-BOCS was not significantly decreased (\( p = .20 \)) from baseline to one week post-infusion, nor was BDI (\( p = .20 \)), although BAI was significantly decreased (\( p = .02 \)). No patient met treatment response criterion (\( \geq 35\% \) Y-BOCS reduction) at one week post-infusion. None reported adverse events.

**Conclusions:** In this small open-label sample, rapastinel was well tolerated and had acute effects on obsessions and compulsions, anxiety and depression. However, rapastinel did not have significant effects on OCD symptoms one week post-infusion.

**Supported By:** Brain and Behavior Research Foundation/NARSAD Ellen Schapiro & Gerald Axelbaum Investigator Award (Dr. Rodriguez), the National Institutes of Mental Health (K23MH092434 [Dr. Rodriguez], K24MH09155 [Dr. Simpson]), the New York Presbyterian Youth Anxiety Center (NYP-YAC), and the New York State Psychiatric Institute (NYSPI). Rapastinel (formerly GLYX-13) study drug was supplied by Naurex (since drug donation, Naurex has been acquired by Allergan). Dr. Rodriguez
received rapastinel for the present study at no cost and she was reimbursed for travel and time to present findings to Allergan after the findings were submitted for publication to American Journal of Psychiatry as a “letter to the editor.”

**Keywords:** Obsessive Compulsive Disorder (OCD), Rapastinel, GLYX-13, Ketamine, NMDAR

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**854. Phase 2 Multisite Double-Blind Placebo-Controlled Trial of TNX-102 SL in Military-Related Posttraumatic Stress Disorder (PTSD): Mediators and Moderators of Treatment Response**

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**Background:** Evidence-based pharmacotherapies are lacking for military-related PTSD. TNX-102 SL* is a proprietary formulation of cyclobenzaprine (CBP) for bedtime sublingual administration that bypasses first pass metabolism and antagonizes 5-HT2A, 1-adrenergic and histaminergic-1 receptors. It is hypothesized to improve PTSD via effects on core symptoms of sleep disturbance and hyperarousal.

**Methods:** Efficacy and safety of TNX-102 SL was investigated in a PTSD population with military-related traumas since 2001 at 24 U.S. clinical sites. Patients were randomized to 12-week treatment with placebo, TNX-102 SL 2.8 mg (TNX2.8) or 5.6 mg (TNX5.6).

**Results:** The primary efficacy analysis comparing TNX2.8 (n=90) to placebo (n=92) was not significant. Yet TNX5.6 (n=49) demonstrated a strong trend towards greater improvement in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) at Week 12 (p=0.053, MMRM; effect size=0.36); sensitivity analyses were significant. Improvements in sleep and hyperarousal occurred early and appeared to mediate therapeutic response. Moderator analyses indicated those with combat PTSD and greater baseline severity were most likely to respond to TNX5.6. The most common adverse event (AE) in the TNX-102 SL arms was tongue numbness (39% in TNX2.8; 36% in TNX5.6), which was generally transient, and never severe. Systemic AEs of somnolence, sedation, headache appeared dose-dependent; rates in TNX5.6 mg were 16%, 12%, 12%, respectively.

**Conclusions:** TNX5.6 mg demonstrated activity over placebo in this multicenter trial in a population with military-related PTSD, one not generally responsive to pharmacotherapies. Mediators and moderators of treatment response unique to TNX-102 SL will be discussed.

**Supported By:** Tonix Pharmaceuticals, Inc.

**Keywords:** PTSD - Posttraumatic Stress Disorder, Cyclobenzaprine, Sleep disturbances, Extinction, Recovery

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**855. Response to Methylphenidate and Atomoxetine in Children with ADHD: Pharmacogenetic Predictors**

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**Background:** Despite inconsistent findings from studies using diverse methodologies and populations, commercial genotyping services have been marketed which recommend specific ADHD treatments. We sought to examine the relationship between several candidate and metabolism genes (DAT1,Dr4, ADRA1, COMT, CYP2D6) and response in children who are treated with OROS methylphenidate (MPH) and atomoxetine (ATX) in a crossover study.

**Methods:** Children (n = 191) with ADHD, ages 6-17 (mean 10.5), participated in a double blind, double-dummy, crossover study comparing MPH (mean dose 54 mg) and ATX (mean dose 1.35 mg/kg). Medication was titrated using a flexible, stepped dose optimization for 3-7 weeks with 2 weeks on optimal dose. Primary outcome was ADHD RS and CGI completed by blind raters.

**Results:** The largest number of youth responded to both medications (49%), with a mean reduction in ADHD RS of 15.5 to ATX and 19.1 to MPH. None of the genetic markers were associated with an excellent response to MPH or ATX (i.e., 50% reduction in ADHD symptoms). However, significant associations between nonresponse (< 30 reduction in ADHD symptoms) to ATX and CYP2D6 were detected. Specifically, odds of non-responding to ATX is 2.4 times higher for CPY2D6 poor metabolizers compared to a non-poor metabolizer.

**Conclusions:** In a crossover study of children with ADHD treated for several weeks, dopaminergic and adrenergic genes were not associated with response to either stimulant or non-stimulant medication, although genetic variation in cytochrome P-450 2d6 pathway was associated with non-response to ATX.

**Supported By:** RO1 MH70564-01

**Keywords:** ADHD, Pharmacogenetics

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**856. Methylphenidate vs. Atomoxetine in Youth with ADHD: Comparative Effectiveness and Preference following Treatment with both Medications**

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**Background:** The majority of youth with ADHD treated with psychostimulant medication experience significant improvement, but a smaller number achieve normalized function. The availability of FDA-approved non-stimulants offers therapeutic alternatives, but more information is needed to guide treatment selection and algorithm development. We compared OROS methylphenidate (MPH) (long-acting stimulant) and atomoxetine (ATX) (nonstimulant) in a randomized, double-blind, crossover study (~6 weeks each, separated by a two week placebo washout).

**Methods:** Multiple-group latent growth curve models were used to estimate the effects of drug (ATX vs. MPH) on block 1 and block 2 changes in ADHD symptoms. Latent transition analyses examined the effect of order on responder status.
Preference was determined under blinded conditions by a combination of direct query, ratings, and chart review.

Results: 232 children ages 7–17 were randomized; 199 completed both treatments. Mean doses were: MPH: 54 mg (18.02); ATX: 1.35 mg/kg (0.47). MPH was associated with nominally greater symptomatic response, which reached significance in block 2 (d = 0.17 (block 1); 0.34 (block 2)). MPH was preferred by more families (51%), but a large minority (34%) preferred ATX. Preference was greater for the medication given first, and when there was excellent

Conclusions: Response to both medications was good to excellent, with a small effect size favoring MPH. The relatively large number of families who preferred ATX, and the fact that ATX did substantially better when given first, have important implications for the development of treatment algorithms.

Supported By: NIIMH RO1MH70564, Ro1-MH70564
Keywords: ADHD, Methylphenidate, atomoxetine

857. A Multiple-Ascending Dose Study of the Neuroactive Steroid SAGE-217

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Background: SAGE-217 is a positive allosteric modulator of synaptic and extrasynaptic GABAA receptors with a pharmacokinetic profile optimized for once daily oral administration. This next generation neuroactive steroid is being investigated for multiple GABA-related indications.

Methods: Thirty-six healthy volunteers were enrolled in a Phase 1, double-blind, placebo-controlled multiple ascending dose (MAD) study of SAGE-217. Subjects were randomized 9:3 and received SAGE-217 oral solution or placebo once daily in the morning for seven days. SAGE-217 doses of 15, 30, and 35 mg were used across three cohorts. After washout, subjects in the 30 mg cohort returned for seven days of evening dosing. Pre-defined stopping criteria were utilized to define the maximum tolerated dose (MTD), and electroencephalogram (EEG) recordings assessed electrical activity in the brain to study target engagement.

Results: SAGE-217 was generally well-tolerated, with no serious adverse events reported during the treatment and follow-up periods. The MTD was established as 30 mg daily by the Modified Observer’s Assessment of Awareness/Sedation (MOAA/S) stopping criterion. SAGE-217 produced concentration dependent pharmacodynamic effects as measured by elevation of beta-band EEG (GABAA receptor modulation) at all doses tested; the EEG effect was observed without diminution after each administration over the 7-day dosing period.

Conclusions: SAGE-217 was well tolerated for morning and evening dosing, with no serious adverse events reported. Reported adverse events were mild or moderate in intensity. Target engagement was observed by EEG. SAGE-217 is currently under development in a Phase 2 program examining indications with GABA-related etiologies, including postpartum depression and essential tremor.

Supported By: Sage Therapeutics, Inc.
Keywords: neuroactive steroid, GABA, Postpartum Depression, positive allosteric modulation

858. Efficacy of Deep Transcranial Magnetic Stimulation for Treatment Resistant Late-Life Depression

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Background: Treatment resistant late-life depression (LLD) is a major public health problem. Newer treatments, such as transcranial magnetic stimulation (TMS), have not been systematically studied in older adults, despite the overwhelming need. Deep TMS (dTMS) may be a particularly efficacious neurostimulation strategy in older adults with depression as the coil can target broader cortical regions and overcome age-related atrophy.

Methods: Adults 60 years of age and older with LLD and prior treatment non-response (mean failed trials 2.9; SD 0.25) were recruited at a university mental health centre; 58 patients were randomized to receive active or sham dTMS using aBrainsway H1 coil that targets the dorsolateral and ventrolateral prefrontal cortex bilaterally, with deeper and wider penetration to the left prefrontal cortex. Treatment parameters were: 6017 pulses per session; 18 Hz; 20 treatments over 4 weeks; 120% resting motor threshold intensity. The Hamilton Depression Rating Scale (HDRS-24) was used to assess symptom severity. The primary outcome was remission (defined as HDRS-24 < 10 and 60% reduction in HDRS-24 scores relative to baseline at two consecutive assessments).

Results: In a modified intention to treat analysis (n=52; 6 subjects received treatment with a different coil), active dTMS treatment led to remission in 40% of patients (10 out of 25), while the sham treatment led to remission in 14.8% (4 out of 27) of the patients (Barnard’s test, p = 0.044).

Conclusions: dTMS with the H1 Coil, using extended sessions, led to a clinically meaningful remission rate in older adults with treatment resistant depression that was superior to sham stimulation.

Supported By: Canadian Institutes of Health Research University-Industry Partnership and Brainsway Ltd.
Keywords: Late Life Depression, rTMS, Deep TMS, Randomized controlled trial

859. It’s Not Just Brain Surgery: An In Depth Look into the Commitment of Patients in an Ongoing DBS Research Trial

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Background: Experimental trials for SCC DBS for Depression are ongoing, with a single team’s experience now exceeding 10 years. In addition to the basic requirements of a closely monitored, experimentally intensive research trial, there are unanticipated events that consume time and resources of the patient and the research team.

Methods: This study reviewed clinical and data collection practices to quantify total hours required for 28 DBS subjects (mean Hamilton at last visit: 8.5). Device and surgery related adverse events were collated. Duration of surgeries for initial implantation, battery replacement, explantation, and reimplantation were tracked.

Results: Patients (53.5% temporarily relocated for the study) reported weekly for clinical visits for 8 months (1 month pre-operative, 7 month post-operative), then biannually for 10 years. Visits consisted of self-reports and clinical assessments. Experiments, neuroimaging, and psychotherapy were also required. There were 28 implantations (mean operating time: 8.56 (SD 1.55) hours and 3 day hospitalization), 8 ex-plantations, 5 re-implantations, and 103 IPG replacements in 9 years. 53 SAEs (23 device related, 13 surgery related) and 42 AEs (6 device related, 5 surgery related) were reported. 16 of the device related SAEs required surgical intervention and repair. As of 2015 availability of a rechargeable battery, now implanted in all of the patients, will significantly decrease the number of IPG replacements.

Conclusions: In anticipation of future trial design and ongoing long term follow up it is important to consider the resource cost to the patients and research team. The workload significantly experimental design, including recruitment, retention of subjects, and team demand.

Keywords: DBS, Data collection, Trial design

860. Selective Attrition May Skew Study Outcomes in Treatment Trials with Suicidal Patients

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Background: Patients with suicidal ideation and behavior are typically excluded from antidepressant trials, and few studies focus on identifying treatment options for this population. Furthermore, the most vulnerable patients are at greater risk for study discontinuation which may influence treatment effectiveness findings. We examined factors distinguishing study drop-outs in elevated suicide risk patients entering an 8-week antidepressant trial.

Methods: Patients had current Major Depressive Disorder (MDD) and suicidal ideation and/or prior suicide attempt, and were randomized to double-blinded treatment with controlled-release paroxetine or extended-release bupropion. Clinical and neuropsychological measures were completed at baseline and trial conclusion. Of 67 subjects with baseline neuropsychological measures randomized to treatment, 10 dropped out prematurely. Completers and drop-outs were compared on demographic, clinical and cognitive characteristics.

Results: Drop-out rate was equivalent across medications, with comparable demographics and baseline severity relative to completers. Drop-outs tended towards more non-native English speakers (2(1) = 3.19, P = 0.07), but did not differ from completers in overall intelligence estimate. Drop-outs had a higher rate of prior suicide attempts (2(1) = 4.96, P = 0.03) and poorer impulse control task performance (t(68) = 2.44, P = 0.02) among drop-outs.

Conclusions: Clinical trials with elevated suicide risk patients have drop-out rates similar to other MDD treatment studies, but the most clinically vulnerable patients appear to be at higher risk for discontinuation. Selective attrition of impulsive patients with past attempt histories suggests those who may benefit most from treatment might be more likely to withdraw, and loss of their treatment response information may bias efficacy estimates. For studies of suicidal populations, additional procedures are needed to retain patients.

Supported By: NARSAD, AFSP

Keywords: Clinical Trials, Suicide, Depression

861. Mood Dependent Effects of Ketamine on REM Eye Movements in Patients with Treatment Resistant Depression (TRD)

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Background: Both REM and NREM sleep are dysregulated in depression. REM dysregulation in MDD is thought to be partially linked to a deficient inhibitory influence of Process-S, leading to increased REM density (RD) and short REM latency (RL). Consistent with its effects on enhanced synaptic plasticity, ketamine increases SWS and early night slow-wave activity (SWA) in patients with TRD. Here we extend the examination of ketamine effects on rapid mood improvement to RD, an important marker of REM sleep in depression.

Methods: Participants (n = 24; f = 13; mean = 41.2 y) with MDD, received a single ketamine infusion (0.5 mg/kg over 40 min). Inclusion criteria were a MADRS score of $\geq$ 22. Ketamine mood responders (n = 9) had a $\geq$ 50% reduction in MADRS score. Polysomnography was performed on patients before (BL) and after (K) ketamine infusion. RD was defined as eye movements/ min (amplitude $>$ 25uv, 0.5-4Hz) within a period (REMP).

Results: Ketamine reduced RD counts more in responders (BL = 2.4 counts $\pm$ 0.75 [x $\pm$ SEM] to K = 1.6 counts $\pm$ 0.44), than in non-responders (BL = 2.0 $\pm$ 0.4 to K = 2.4 $\pm$ 0.49; two way ANOVA, F = 5.25, df 1, 22; p = 0.0148). Baseline vs. post ketamine RD1 change scores correlated with MADRS change scores (r = 0.21, p = 0.024). Effects were limited to REMP1.

Conclusions: Ketamine decrease of RD is consistent with RD associated with sleep need and homeostasis, and with ketamine’s capacity to increase SWA in TRD. Both REM density and SWA may be useful biomarkers for exploring ketamine’s rapid antidepressant effects.

Supported By: Intramural Research National Institute of Mental Health

Keywords: Treatment Resistant Depression, REM sleep, REM Density, synaptic plasticity
862. Patient Report with the Suicide Ideation and Behavior Assessment Tool (SIBAT): Acceptability and Sensitivity to Rapid Change

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Background: Clinicians and patients provide complementary perspectives for suicidality assessment. The SIBAT (an instrument pending FDA review) incorporates both in separate modules. Here, we focus on patient-driven aspects of the instrument. We demonstrate (1) the SIBAT’s acceptability and comprehensibility for individuals at risk for suicide and (2) the sensitivity of the instrument’s primary self-report module (My Current Thinking [MCT]) to changes in suicide-related thoughts.

Methods: Cognitive interviews were performed with 14 adults from a psychiatric clinical research setting, 686 adult members of a distributed online community, and 10 adolescents (ages 12-17) from the Emergency Department (ED) of a southeastern Children’s Hospital. All patients had a history of suicidal ideation and/or behavior or were self-identified as being at risk for suicide. Sensitivity of MCT was assessed within the context of a clinical trial (n=66) for medication being evaluated for the treatment of patients with Major Depressive Disorder at imminent risk of suicide.

Results: Adults and adolescents found the instrument acceptable and comprehensible. MCT demonstrated acceptable internal consistency (0.9284) as well as impressive sensitivity to adaptive changes in thinking related to suicidal ideation and behavior at 4 hours and 24 hours after initiation of treatment (both p < .0001). MCT appeared sensitive to differences between treatment groups at the same intervals.

Conclusions: The SIBAT has been found to be comprehensible and acceptable by a range of relevant patients. Its primary patient-report scale has shown utility for differentiating, rapid changes in thinking related to suicidal ideation in patients receiving ED-based treatment.

Supported By: Janssen Scientific Affairs, LLC

Keywords: Suicide, Assessment, Suicidal ideation, Clinical Trials

863. Docosahexaenoic Acid Supplementation Increases Cortical White Matter Microstructural Integrity in Medication-Free Youth with ADHD: A Placebo-Controlled Diffusion Tensor Imaging Study

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Background: Cross-sectional evidence indicates that children with ADHD exhibit lower blood levels of docosahexaenoic acid (DHA), the most abundant omega-3 fatty acid in mammalian brain, and widespread deficits in brain white matter integrity (WMI). This randomized double-blind placebo-controlled trial investigated the effects of DHA supplementation on WMI in children with ADHD. Our a priori prediction was that DHA would be more effective than placebo for increasing WMI.

Methods: Medication-free children (mean age 9.6 years, n=20) with ADHD were randomized to placebo or DHA (1,200 mg/d) for 10 weeks. Corpus callosum (CC) WMI by diffusion tensor imaging (DTI) and erythrocyte DHA levels were determined at baseline and endpoint.

Results: The majority of patients were male and stimulant-naive. DHA levels increased significantly in patients receiving DHA but not placebo. Significant baseline-endpoint reductions in mean diffusivity (−17%, p=0.04, d = 1.0) and radial diffusivity (−26%, p=0.04, d = 1.1) were observed in the left CC of patients receiving DHA, whereas little change in mean diffusivity (−2%, p=0.42, d = 0.12) and radial diffusivity (−9%, p=0.29, d = 0.29) was observed in patients receiving placebo. There was a trend with a medium effect size for an increase in fractional anisotropy in the left CC of patients receiving DHA (+13%, p=0.1, d = 0.67) but not placebo (+4%, p=0.34, d = 0.22).

Conclusions: Based on prior animal evidence that demyelination or dysmyelination are associated with elevated radial diffusivity, the present findings suggest that DHA supplementation improves myelin integrity in the left CC of children with ADHD.

Supported By: Royal DSM Nutritional Products, LLC

Keywords: ADHD, Omega-3, White matter, DTI

864. The Effects of Four Weeks of Intranasal Oxytocin on Social Responsiveness and Repetitive and Restricted Behaviors in Autism Spectrum Disorders: A Randomized Controlled Trial

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Background: Autism spectrum disorders (ASDs) are characterized by impairments in social interaction and repetitive and restricted behaviors (RRBs). To date, no pharmacological treatment exists targeting the core symptoms of ASD, yet the pharmacological use of the neuropeptide oxytocin (OT) has gained interest from the research community to explore its potential for elevating social deficits in ASD.

Methods: A double-blind randomized placebo-controlled trial with thirty-four young adult men with ASD (17 OT/17 Placebo) was conducted to assess behavioral effects of OT therapy (i) at baseline; (ii) after four weeks of therapy; and (iii) four weeks post-treatment (follow-up). Doses of 24 IU oxytocin (Syntocinon®ii, Sigma-tau) or placebo nasal spray were administered daily for four weeks. Primary outcome measures included the social responsiveness scale (SRS) and the repetitive behavior scale (RBS-R). Secondary outcome measures included questionnaires assessing attachment, mood state and quality of life.

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Results: After four weeks of OT administration, self-reports on RRBs showed tentative reductions in the OT group (F (1,31)=3.83, p=0.06) and this effect persisted until one month after treatment F(1,31)=4.02, p=0.05. No significant changes in social responsiveness were observed immediately after the four-week OT treatment, but interestingly, at the 1-month follow-up session, significant improvements were revealed for the informant-based SRS report, indicating clear improvements in reports of social motivation (F(1,22)=4.71, p=0.04) and social communication (F(1,22)=7.39, p=0.01). For the secondary outcome measures, only tentative effects were revealed.

Conclusions: The observed improvements after the four-week OT treatment in social responsiveness and RRBs indicate that OT can induce long-term behavioral changes in individuals with ASD.

Supported By: Flanders Fund for Scientific Research (FWO), Branco Weiss Fellowship of the Society in Science - ETH Zurich, Marguerite-Marie Delacroix foundation

Keywords: Autism Spectrum Disorder, Oxytocin, Social Functioning, Repetitive and Restricted Behaviors

865. Initial PTSD Symptoms Predict Persistent Pain among Survivors of Major Thermal Burn Injury

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Background: Persistent pain and posttraumatic stress disorder (PTSD) are common, morbid outcomes among survivors of major thermal burn injury (MThBI) and significantly affect survivor quality of life. Accumulating evidence suggests that mechanisms leading to persistent pain are related to neuroinflammatory mechanisms which are also involved in the pathogenesis of PTSD. In addition, PTSD symptoms may drive neurobiologic changes which contribute to the persistence of pain. For these reasons, we hypothesized that PTSD symptoms in the early aftermath of MThBI would predict persistent pain outcomes.

Methods: To test this hypothesis, we examined the relationship between PTSD symptoms (PTSD Symptom Scale Interview) assessed within 72 hours of hospital admission and MThBI pain outcomes (0-10 NRS) over time in a cohort of MThBI survivors (n = 96) admitted to one of three burn centers.

Results: In a linear mixed regression model adjusted for age, sex, and ethnicity, initial PTSD symptom severity predicted pain severity across outcome timepoints during the year following MThBI (β = 0.03, p = 0.03). In addition, pain and PTSD symptom severity outcomes were correlated (6 weeks: r = 0.22, p = 0.03; 12 months: r = 0.31, p = 0.04).

Conclusions: These data support the hypothesis that PTSD symptoms in the early aftermath of MThBI predict pain outcome, and that PTSD and pain outcomes after MThBI are associated over time. Further studies are needed to understand pathophysiologic mechanisms accounting for the relationship between PTSD and pain outcomes in MThBI survivors.

Supported By: UNC Department of Anesthesiology, DC Firefighters Burn Foundation

Keywords: PTSD - Posttraumatic Stress Disorder, Chronic pain, Burn Injury

866. Relationship between Antipsychotic Blood Levels and Treatment Failure during the CATIE Study

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Janssen Research & Development

Background: Antipsychotic blood levels (ABLs) may help identify patients at risk for treatment failure. Reference ranges (RR) for plasma concentrations of ABLs that account for between-subject variability were developed for risperidone and olanzapine based on population pharmacokinetic models. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) collected clinical outcomes and ABLs, allowing testing of the relationship of ABLs with outcomes in patients with schizophrenia.

Methods: ABLs from 348 subjects who were randomized to olanzapine or risperidone during phase 1 and 2 of CATIE were compared to the 80% RRs and were assessed as below or within/above the RR. Treatment failure was defined according to the following criteria: (1) emergency room visit for psychiatric reasons, (2) hospitalization for psychiatric reason, (3) adverse event of completed suicide, suicidal ideation, or suicide attempt, (4) assaultive behavior, (5) being arrested or jailed (6) 2 point increase from baseline in CGI-S score, (7) 25% increase in Positive and Negative Syndrome Scale total score.

Results: Treatment failure was assessed in 323 subjects and occurred in 126 subjects. The proportion of subjects with ABLs below RR was 18.3% (59/323) compared to 10% expected in a fully adherent population. Among the 59 subjects with ABLs below RR, 50.8% had treatment failure (compared to 36.4% for the 264 subjects with ABLs within/above RR). The difference between groups was statistically significant (odds ratio=1.810; 95% CI=1.025 to 3.197; p value=0.0408).

Conclusions: The analysis of CATIE data showed that ABLs can be used as an indicator to detect the risk of relapse.

Supported By: Janssen Research & Development

Keywords: Antipsychotics, Drug Levels, Treatment Failure

867. Efficacy and Safety of Paliperidone Palmitate 3-Month Formulation Vs Placebo for Relapse Prevention of Schizophrenia: Treatment Effect Using a Number Needed to Treat Analysis

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Janssen Research & Development, LLC
Background: In a randomized clinical study, paliperidone palmitate 9-month formulation (PP3M) significantly delayed time to relapse in patients with schizophrenia. The hazard ratio comparing PP3M with placebo was 3.45 (95% CI: 1.73, 6.88), demonstrating superiority of PP3M in preventing relapse. Number needed to treat (NNT) and number needed to harm (NNH) analyses provide an alternative approach to assess the magnitude of treatment effect and can provide valuable additional information on therapeutic gain.

Methods: Number needed to treat to prevent relapse at months 6 and 12 was calculated using data from randomized clinical trial (NCT01529515) of PP3M versus placebo. Number needed to harm was also calculated for extrapyramidal symptoms (EPS) at the end of double-blind phase.

Results: The NNTs (95% CI) to prevent relapse at months 6 and 12 were 4.1 (2.6, 9.4) and 2.3 (1.4, 7.1) for PP3M. NNHs reported for dyskinesia, akathisia, tremor, weight gain and use of anticholinergic were 178.5, 27.1, 80.0, 18.9 and 43.8 respectively. NNH for overall EPS was 21.4.

Conclusions: The single digit values of NNT to prevent relapse suggest that PP3M could benefit patients. Similarly, the relatively high NNH value suggests that the risk of EPS is reasonably low.

Supported By: Janssen Research & Development LLC

Keywords: NNT, Long acting injectable, EPS, Safety

868. Early Intervention in Attenuated Psychosis Syndrome: A Phase II Study Evaluating Efficacy, Safety, and Tolerability of Oral BI 409306

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Background: Patients with attenuated psychosis syndrome (APS) (often adolescents) exhibit motor, emotional, cognitive, and behavioral alterations between those of healthy individuals and those with psychotic disorders. BI 409306, a potent and selective phosphodiesterase-9 inhibitor that may improve N-methyl-D-aspartic acid (NMDA) signaling, is under development for early intervention in APS.

Methods: We describe the design of a 52-week proof-of-concept study, investigating the efficacy, safety, and tolerability of BI 409306 vs placebo.

Results: This will be a multinational, double-blind, parallel-group study. Eligible patients with APS will be 16–30 years of age, with a screening risk profile based on the North American Prodrome Longitudinal Study (NAPLS) algorithm indicative of >35% conversion rate to psychosis within 52 weeks. Overall, 300 patients are planned for randomization (1:1) to oral BI 409306 or placebo for 52 weeks (4-week follow-up). The primary endpoint will be time to first episode psychosis (FEP), assessed by positive symptoms in the psychotic range. Secondary endpoints include change from baseline on the Schizophrenia Cognition Rating Scale (ScORS) total and the composite score of Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (24 and 52 weeks). Safety will be assessed based on physical examination, vital signs, laboratory tests, electrocardiogram, suicidality, extrapyramidal symptoms, and adverse events.

Conclusions: This will be one of the first studies to test a novel drug mechanism as an early intervention in APS, with the statistical power to detect a significant treatment effect vs placebo on the conversion rate to FEP. Recruitment is planned to start in 2017.

Supported By: Study funded by Boehringer Ingelheim. Editorial assistance was provided by Lisa Auker of Fishawack Communications, and was funded by Boehringer Ingelheim.

Keywords: Attenuated psychosis syndrome, First Episode Psychosis, High-risk, Neuroplasticity

869. Computational Modeling of Approach Avoidance Behavior in Individuals with Positive and Negative Valence Domain Dysfunction Reveals Distinct Speed/Accuracy Trade Off

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Background: Mood and anxiety disorders are heterogeneous and their underlying pathology is complex. The Research Domain Criteria approach seeks to establish dimensionally and neuroscience-based descriptions of psychopathology that may inform better classification and treatment approaches. Computational Psychiatry is an emerging field that utilizes mathematical approaches to delineate dysfunctions in behavioral processing in psychiatric populations.

Methods: n=57 (42 females) individuals from an ongoing study (1R01MH101453) of individuals with mood and anxiety problems completed an implicit approach avoidance task. We used a drift-diffusion modeling approach, which aims to decompose reaction times and accuracy of responding into (a) non-decision time, (b) speed of processing, and (c) response threshold, based on the fast-dm-30 algorithm. Specifically, each approach/avoidance domain (positive, neutral, disgust, and angry) was modeled with a unique speed of processing (v) and response threshold (a) parameter.

Results: A principal components analysis of the drift diffusion parameters revealed that most of the variance of the behavior was accounted for by two components that separated along (1) avoidance accuracy of both positively and negatively valenced stimuli and (2) approach accuracy and speed of positively and negatively valenced stimuli. The accuracy model parameters correlated significantly with standard approach/avoidance measures. Finally, induction-time was significantly correlated with anxious arousal.

Conclusions: These preliminary data show that computational approaches can be used to decompose behavioral processing on an approach/avoidance task into...
870. Induced Anxiety Leads to Underestimating Time

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Background: Our subjective experience of time is an integral part of our mental life and is intimately linked to our emotional state. Hedonic events are associated with quick passage of time but the picture is less clear for negative experiences. For example, during an anxiety-provoking interview time might fly but during traumatic events it might be reported that time froze. However, no study up to date has investigated how anxiety affects time perception.

Methods: In two experiments we used threat of unpredictable shock to induce anxiety in healthy individuals performing two-alternative forced choice tasks, a subsecond (Experiment 1, n=25) and a suprasecond (Experiment 2, n=25) temporal bisection paradigm. Specifically, participants viewed stimuli that remained on the screen for different time intervals (Experiment 1: 300-700ms, Experiment 2: 1400-1600ms) and then decided whether their duration was “short” or “long” compared to anchor durations they had in mind.

Results: In line with our hypothesis, in both experiments, participants significantly underestimated time in the anxiety condition, as indicated by a rightward shift of the psychophysical function. Factors that affected this effect are discussed.

Conclusions: Our results are in line with the idea that anxiety is associated with the underestimation of time. Future studies could explore the possibility that during a fearful event, time might freeze (i.e. time overestimated) in line with reports that this is so under threat of imminent physical harm. This line of research might help explain day-to-day difficulties of anxious individuals in everyday tasks that involve keeping track of time.

Supported By: Wellcome Trust

Keywords: Anxiety, Time Perception, Psychophysics, Emotion perception

871. Modulation of the Insula and Somatosensory Cortex by Ondansetron

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Background: Ondansetron is a 5-HT3 receptor antagonist used to treat nausea and vomiting. In addition to its potent anti-emetic effects, ondansetron reduces neuropathic pain and pruritus, and small trials have found reductions in overall symptom severity in obsessive-compulsive and Tourette’s disorders. Despite these promising data, the neural mechanisms underlying ondansetron’s effects are unknown. Here we investigated the effects of ondansetron on brain activation using fMRI in order to test the hypothesis that modulation of activity in insula and somatosensory regions may underlie the drug’s efficacy in treating a variety of psychiatric and sensory conditions.

Methods: Data were analyzed from 40 healthy controls using a double-blind placebo-controlled single-dose challenge design to examine the effects of 8 (n=12), 16 (n=15), or 24 (n=13) mg of ondansetron on brain function. Subjects performed an fMRI task previously shown to elicit activation in insula and somatosensory cortex. Preliminary analysis examined changes in activation for ondansetron vs. placebo in each dose group separately using whole-brain t-tests at a threshold of p<0.05 (uncorr).

Results: 24-mg ondansetron was associated with reduced activation in bilateral somatosensory cortex, mid-posterior insula, premotor areas, and prefrontal cortex compared to placebo. Activity in left somatosensory regions was also reduced for the 16 and 8-mg doses, although effects were much less widespread than for the 24-mg dose.

Conclusions: Results from these preliminary analyses point to a dose-dependent reduction of somatosensory and insula activity with single doses of ondansetron. These findings suggest that high-dose ondansetron could be useful in treating disorders associated with hyperactivation of these regions.

Supported By: R21MH107589 (NIMH)

Keywords: Insula, somatosensory, OCD, sensory processing, pharmaco-fMRI

872. Mechanisms of Peer Influence on Decision-Making in Adolescence

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Background: In general, adolescence is characterized by a high degree of physical health. Health dangers mostly emerge by decisions teenagers themselves make: Epidemiological research has found higher rates of unprotected sexual intercourse, risky driving, delinquency and experimenting with drugs in adolescence as compared to any other period in life. Previous research also emphasizes the important impact of social factors, i.e. peers, on these maladaptive behaviors. However, mechanisms which underlie the influence of peers on decision-making in adolescents are so far poorly understood.

Methods: We use two social decision-making tasks in combination with behavioral computational modeling in adolescents (n=30, 12-14y) and young adults (n=30, 20-32y). In a within-subjects-design, both age groups underwent the task once while interacting with a peer or a player of the other age group.
873. Dissociable Temporal Effects of Bupropion on Behavioural Measures of Emotional and Reward Processing in Major Depressive Disorder

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Background: Early in treatment serotonergic and/or noradrenergic antidepressants remEDIATE negative biases in information processing observed in major depressive disorder (MDD). However, it remains unclear whether dopaminergic antidepressants exert similar early actions on information processing. Here we investigate the early and longer-term effects of bupropion on behavioural measures of emotional and reward processing in MDD.

Methods: 41 MDDs and 40 healthy controls (HCs) participated in a repeated measures study involving open-label administration of bupropion to just the MDDs over 6 weeks. All participants completed the Emotional Test Battery and a reward task at baseline, week 2 and week 6.

Results: Only the bupropion-treated MDDs displayed a significant decrease in the misclassification of faces as sad (F1, 80 = 4.09, p < 0.05; t41 = 2.72, p < 0.05) and false recall of negative self-referent words (F1, 81 = 5.73, p < 0.05; t42 = 2.12, p < 0.05) between baseline and week 2. Conversely, bupropion was found to significantly worsen performance on the reward task between baseline and week 2 (t14 = 4.17, p < 0.01) prior to normalisation to HC level at week 6 (t14 = -10.5, p < 0.001; t28 = -0.25, p = 0.80).

Conclusions: Early in treatment bupropion does act to reduce negative biases in emotional processing but may worsen reward processing with the beneficial actions only occurring later in treatment. Such dissociation in the temporal effects of bupropion on emotional and reward processing has implications in the treatment of the different symptom domains of negative affect and anhedonia in MDD.

Supported By: J&J

Keywords: Major Depression, Bupropion, Emotional processing, Reward processing

874. Pathways to Late-Life Suicidal Behavior: Cluster Analysis and Predictive Validation

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Background: Clinical heterogeneity is a key challenge in understanding suicidal risk, and distinct pathways to suicidal behavior are likely to exist. We aimed to identify pathways as indicated by latent classes of late-life depression cases, relating them to the history and characteristics of suicidal behavior.

Methods: Cluster analysis was performed on four cognitive/decision-making, eleven personality/social support variables, and depression severity. Predictive validation was assessed via the individuals’ past and prospective (30 months) suicidal ideation and behavior. Sample: 189 depressed elderly (60+), and 57 non-psychiatric controls.

Results: The cluster analysis selected five-clusters, three of which conferred high suicide risk: 1) Combination of cognitive deficits, personality and environmental risk factors, low delay discounting, 100% with attempt or ideation at baseline, majority with high- lethality attempts; 3) Cognitive deficits and exaggerated delay discounting, 87% with attempt and ideation; and 4) Personality-pathology based cluster (i.e. low self-esteem), minimal cognitive deficits, 82% with attempt or ideation at baseline, 12% with high- lethality attempts. In contrast, Cluster 2 participants had uniformly lower risk scores, 32% with suicidal ideation or attempt at baseline. There were significant between-cluster differences in the number of emergency hospitalizations during follow-up, as well as the number (p<0.001) and lethality (p=0.002) of suicide attempts prior to baseline, and during follow-up (p=0.006, 30 attempts by 22 participants, two of them lethal).

Conclusions: Combinations of known risk factors define distinct pathways to suicidal behavior in late-life depression. This analysis identified five subgroups of depressed participants ranging from extremely high risk for fatal suicide attempts to subgroups with much lower suicide risk.

Supported By: National Institutes of Mental Health R01 MH085651

Keywords: Late-life, Suicide, Cluster Analysis, Predictive Validation, Decision Making

875. Differences in Neural Activation during Implicit Facial Emotion Processing in Youth and Adults with Bipolar Disorder

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Background: Poor judgment of emotional facial expression is a well-established feature of bipolar disorder (BD). Few studies have explored changes in the neural circuitry of emotion processing across the lifespan in BD. This cross-sectional study compared functional activation in fronto-limbic regions during a task of implicit emotion processing in youth and adults with BD.

Methods: 26 adults (19 with BD and 7 healthy controls (HC) aged > 18), and 18 children (aged <17, 9 with BD and 9 HC) underwent an fMRI evaluation involving an implicit face processing paradigm. Participants were asked to identify the color of dynamically changing faces displaying positive or negative emotions. Based on previous findings we performed region-of-interest (ROI) analyses in the superior temporal gyrus (STG), inferior frontal gyrus (IFG), cingulate cortex, cuneus, and amygdala. Data was analyzed by conducting mixed factorial ANOVAs to compare activation patterns across emotion condition between HC and BD, across age groups. Bonferroni correction accounted for multiple testing.

Results: Reaction times and accuracy levels were comparable across age and diagnostic groups. Relative to adult HC, adults with BD showed significantly greater activity in the anterior cingulate cortex and STG (p<.05) in response to negative emotions. By comparison, children with BD activated a greater number of regions including STG, cuneus, IFG, and amygdala (p<.05).

Conclusions: The neural correlates of negative emotion processing undergo substantial development across the lifespan. This may be due to a different developmental trajectory in regions implicated in emotion processing in BD relative to HC.

Supported By: Dunn Foundation
Keywords: Bipolar Disorder, Affective Processing, brain (or fMRI), lifespan

876. Brain Network Functional Connectivity and Cognitive Performance in Major Depressive Disorder

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Background: Major depressive disorder (MDD) is one of the most prevalent and debilitating psychiatric disorders. Cognitive complaints are commonly reported in MDD and cognitive impairment is a criterion item for MDD diagnosis. As cognitive processes are increasingly understood as the consequences of distributed interactions between brain regions, a network-based functional connectivity approach may provide novel information about the neurobiological basis of cognitive deficits in MDD.

Methods: 54 Depressed (MDD, n = 24) and non-depressed (control, n = 30) adult participants completed neuropsychological testing and an MRI session including rest-state fMRI (rsfMRI). Neuropsychological assessments were used to calculate cognitive domain scores (processing speed, working memory, episodic memory, and executive function). Anatomical regions of interests were entered as seeds for functional connectivity analyses in three cognitive networks: default mode, salience, and executive control. Partial correlations controlling for age and sex were conducted for cognitive domain scores and functional connectivity in clusters with significant differences between groups.

Results: Significant rsfMRI differences between groups were identified in multiple clusters for each network. Processing speed and working memory scores were inversely correlated with connectivity in the default mode network in the MDD group. Processing speed was positively correlated with connectivity in the executive control network in the MDD group. There were no significant correlations between functional connectivity and cognitive domain scores in the control group.

Conclusions: These results provide evidence that cognitive performance in MDD may be associated with aberrant functional connectivity in cognitive networks and suggest patterns of alternate brain function that may support cognitive processes in MDD.

Supported By: R01 MH077745, K24 MH110598
Keywords: Major Depressive Disorder (MDD), Cognitive Performance, Functional connectivity, Functional MRI, Mood disorder

877. Effects of Acute and Early-Life Stress on Reward Learning Behavior

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Background: Convergent cross-species evidence suggests that stress-induced anhedonia may be one mechanism underlying associations between both acute and early-life stress (ELS) and psychopathology. However, no research has examined whether acute stress may differentially impact reward-related behavior among those who were exposed to ELS.

Methods: Female community participants who reported elevated ELS (N=37) and well-matched controls (N=28), completed a probabilistic reward task following a laboratory manipulated acute stressor, or a control condition, on two separate days (order counterbalanced). Response bias, the modulation of behavior as a function of reward history, was the primary behavioral variable of interest. Cortisol and self-reported state affect were collected throughout sessions.

Results: The acute stress manipulation increased anxiety, negative affect, and cortisol (all ps<.005). Results replicate prior observations of acute-stress induced reductions in response bias (p=0.001). This was driven by increased accuracy to low expected-value (EV) stimuli. No effect of acute-stress on high-EV stimuli accuracy was observed. Further, overall accuracy was elevated in the stress condition. Lastly, there were no main or interactive effects of ELS on response bias.

Conclusions: We provide further replication of acute-stress induced reductions in response bias. However, contrary to prior reports, acute-stress did not reduce high-EV stimulus accuracy. Thus, we cannot rule-out acute-stress induced increases in performance, as opposed to induced impairments.
878. Brain Connectivity as a Target for Medication Development for Impulsivity
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**Background:** Functional magnetic resonance imaging of brain connectivity has emerged as a tool to study behavioral disorders. This session will discuss results of studies examining effective brain connectivity related to impulsivity as a tool to gather initial data on effects of medications on relevant brain circuitry in humans.

**Methods:** Effective connectivity was determined during a Go/No-go task with two levels of difficulty (Easy and Hard) in cocaine dependent participants and non-drug using controls as measured by dynamic causal modeling (DCM) in SPM.

**Results:** Although performance on the Go/No-Go task was not significantly different between cocaine dependent participants and controls, DCM analysis revealed that prefrontal–striatal connectivity differed between the groups. During successful inhibition during the Hard NoGo condition in controls, the effective connectivity from right dorsolateral prefrontal cortex (DLPFC) to L caudate became more positive, suggesting greater top-down control. However, in cocaine dependent participants, there was no significant change in DLPFC to caudate connectivity during the Hard No-go task.

**Conclusions:** Effective brain connectivity related to impulsivity differs between groups that clinically have high impulsivity and controls. These differences in connectivity are a potential target for medication development and will be discussed in light of ongoing studies 5-HT2CR agonist and a 5-HT2AR antagonist, and how this research methodology could inform future clinical trials that can be submitted to the FDA for indications for treatment of impulsivity.

**Supported By:** U54DA038999, P50DA033935

**Keywords:** Impulsivity, Serotonin, effective connectivity

879. Temporal Discounting at Age 14 Predicts Cannabis Use at Ages 16 and 18
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**Background:** Greater temporal discounting has been associated with a range of problematic impulsive behaviors including substance abuse, obesity, and pathological gambling. It is not known whether greater temporal discounting precedes or is an effect of these behaviors. Here we examine temporal discounting and cannabis use in a large longitudinal sample of adolescents collected by the IMAGEN consortium (http://www.imagen-europe.com).

**Methods:** Individual temporal discounting rates measured by Kirby’s Monetary Choice Questionnaire and lifetime use of cannabis estimated by the European School Survey on Alcohol and Other Drugs (ESPAD) was assessed at three time points: 14, 16, and 18 years old. Complete data at each timepoint was available in 1120 adolescents. The bidirectional relationships between these two variables across time were examined using an autoregressive cross-lagged model in Mplus.

**Results:** The overall model fit was good ($\chi^2=0.16$, $df=2$, $p=0.9$; RMSEA = 0.001; CFI = 1.0). There were three main findings: i) stability paths for temporal discounting and cannabis use were significant across time, ii) temporal discounting and cannabis use were significantly correlated at each time point, and iii) temporal discounting significantly predicted future cannabis use but cannabis use did not predict future rates of temporal discounting.

**Conclusions:** The results are consistent with the notion that impulsivity is a cause rather than an effect of cannabis use. Early interventions which lower temporal discounting in impulsive adolescents may be an effective investment against future problematic drug use.

**Supported By:** This work was funded by EU Framework 6 and the National Institute on Drug Abuse (NIDA) grant 1R21DA038381, Support was also provided by an NIH grant 1P20GM103644-01A1 awarded to the Vermont Center on Behavior and Health.

**Keywords:** Temporal discounting, Impulsivity, Cannabis, Substance use, Adolescents

880. Uncovering the Role of Specific Orbitofrontal Circuits in Decision-Making
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**Background:** The orbitofrontal cortex (OFC) is critically involved in adaptive decision-making and OFC dysfunction has been linked to inflexible behavior in several mental disorders. The OFC sends dense projections to multiple subcortical targets and it is unknown whether distinct OFC circuits mediate different aspects of decision-making processes that may be involved in the pathophysiology of schizophrenia and addiction.

**Methods:** To determine the role of specific OFC circuits in decision-making, we used a novel viral approach combining a floxed diphtheria toxin receptor and a retrograde Cre-expressing virus to target OFC neurons that project selectively to the nucleus accumbens (N=20) or the amygdala (N=20). Rats were trained on a three-choice, probabilistic reversal-learning (PRL) task and then received an injection of saline or diphtheria toxin (DT; 30 ug/kg). Since rats do not express DT receptors, administration of DT causes selective ablation in those OFC projection neurons that...
express DT receptors. Decision-making was then reassessed in the PRL task.

**Results:** Ablation of OFC neurons projecting to the nucleus accumbens impaired the ability of rats to flexibly adjust their decision-making in the PRL by reducing the influence of negative outcomes on decision-making. In contrast, ablation of OFC neurons projecting to the amygdala improved PRL performance by increasing the influence of positive outcomes on future decision-making.

**Conclusions:** These data indicate that distinct OFC circuits mediate dissociable components of decision-making. By combining sophisticated viral approaches with translationally analogous behavioral assessments, these data suggest that decision-making may be a useful biomarker for understanding OFC pathophysiology in mental disorders.

**Supported By:** R01 DA043443; T32 MH14276

**Keywords:** Orbitofrontal Cortex, reversal learning, corticolimbic, Impulsivity, Decision Making

881. Quantifying Social Interaction in Borderline Personality Disorder

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**Background:** People with Borderline Personality Disorder have social attributions that are extreme and often difficult to revise. Negative attribution bias has been previously demonstrated. We extend this work by quantifying social behaviors in two interactive contexts: first, regulation of interpersonal space (social distance task), and second, reward learning for social and non-social cues (social valuation task, SVT).

**Methods:** Female BPD and control subjects interacted with a confederate for both tasks. Between-group behavior was compared using t-tests and mixed-effects models. We tested for relationships between behavior and psychological variables with Pearson’s correlations.

**Results:** Preferred social distance was two-fold greater in BPD versus control (control n=30, mean=11.03”, SD=5.7; BPD n=23, mean=21.11”, SD=11.75; t=-4.12, p<0.001).

However, in the BPD group, preferred distance does not correlate with mood, anxiety, impulsivity, or BPD symptoms (p>0.05), and preferred distance does not differ by medication status or by previous diagnosis (p>0.05). In the SVT, there were significant group x predictor effects revealing less weight on non-social and more weight on social predictors in BPD (p< 0.0005).

**Conclusions:** Interactive social tasks allow us to precisely define differences and similarities in social behavior and learning in BPD, extending psychological theory and previous non-interactive methods. Quantitative markers of social deficits in BPD will allow us to measure the efficacy of current interventions (using markers to track treatment), define sub-groups that may respond differentially to treatment (using markers to predict outcome), and investigate relevant brain networks to develop neural targets for intervention (using markers as probes for key circuits).

**Supported By:** NARSAD Young Investigator Grant

**Keywords:** Social Cognition, Borderline Personality Disorder, Reinforcement learning

882. The Relationship between Catastrophizing, Perception of Disability, and Memory in Veterans with Chronic Pain

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**Background:** Chronic pain is associated with a variety of psychiatric symptoms including depression and suicide. Memory difficulties also are a primary complaint among people with chronic pain. Most research to date has focused on pain intensity, with results showing that more severe or intense pain is related to more impaired memory. Limited research has focused on negative cognition (catastrophizing or negative thinking patterns) as a contributor to memory deficits in patients with chronic pain. This study will examine cognitive factors of pain (i.e., catastrophizing and perception of disability) that may impact memory.

**Methods:** Participants included 80 veterans (mean age = 36.93, 82.5% male) from the Salt Lake City area. Participants completed pain measures (McGill Pain Inventory, Pain Catastrophizing Scale, and the Pain Disability Scale) and the CVLT-II to assess memory and learning. Bivariate correlations were utilized to assess the relationship between pain characteristics and learning, short-term, and long-term memory.

**Results:** Pain catastrophizing was negatively related to learning (Trials 1-5, p=0.007) and memory (short free recall, p=0.006 and long free recall, p=0.016). Perceived disability due to pain was negatively related to learning (Trials 1-5 p=0.043) and memory (short free recall, p=0.019 and long free recall, p=0.010).

**Conclusions:** These findings suggest that pain intensity alone may not sufficiently describe the cognitive concerns among people with chronic pain. Pain and memory have been shown to share common central nervous system pathways (Liu et al., 2000); as such, research examining these common pathways may provide new insights for improved treatment approaches.

**Supported By:** 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; Merit Review 5I01CX000253-02

**Keywords:** Memory, chronic pain, catastrophizing, perceived disability

883. Is Categorical Perception of Syllables Intact in Long-Term and First-Episode Schizophrenia?

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**Background:** Schizophrenia is associated with deficits in language processing, thought to reflect left frontal and temporal cortex abnormalities. Positive symptoms tend to be
associated with temporal cortex gray matter loss, and negative symptoms with prefrontal gray matter loss. The degree to which language deficits are due to impaired memory-based categorical perception, and whether such abnormalities are present at first psychotic break are unknown.

**Methods:** We investigated categorical perception of syllables in 19 long-term schizophrenia individuals (Sz; min 5 years illness duration) and 20 matched controls (HCSz), and 21 individuals at their first-episode of schizophrenia (FE; within 2 months) and 19 matched controls (HCFE). Participants were presented with nine artificial syllables varying in 5ms increments of voice-onset time (VOT) along the Ba-Pa continuum. VOT ranged from 0ms (strong Ba) to 40ms (strong Pa). Participants decided whether the syllable was “Ba” or “Pa”.

**Results:** Linear regression tested whether Sz and FE utilized more linear (and less categorical) perception. There were no significant differences in regression coefficients for Sz compared to HCSz (effect size d=0.01), or for FE compared to HCFE (d=0.12). However, FE individuals who showed more linear perception were more symptomatic on PANSS positive symptoms, thought disturbance, and paranoid-belligerence factors (r=0.49). However, FE individuals who showed more linear perception were more symptomatic on PANSS positive symptoms, thought disturbance, and paranoid-belligerence factors (r=0.49).

**Conclusions:** The behavioral data suggest no significant group-level deficits in the categorical perception of syllables in schizophrenia. However, the ability to categorically perceive syllables at first-episode is related to positive symptoms, suggesting subtle deficits in linguistic processing early in disease course, likely related to pathophysiology of left temporal cortex.

**Supported By:** NIH R01 MH094328

**Keywords:** Schizophrenia, First-Episode Psychosis (FEP), categorical perception, phoneme, voice onset time

884. Plasma Cholesterol Correlates Negatively with Positive Symptoms of Schizophrenia

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**Background:** N-methyl-D-aspartate receptors (NMDARs) have been implicated in the etiology of symptoms of schizophrenia. 24S-hydroxycholesterol, a major brain cholesterol metabolite, has been found to be a modulator of NMDAR. However, the relationship between peripheral plasma cholesterol and psychotic symptoms has not been adequately evaluated in patients with schizophrenia. This study evaluates the relationship between plasma cholesterol and psychotic symptoms in patients diagnosed with schizophrenia.

**Methods:** We recruited 39 Adult patients diagnosed with Schizophrenia [mean age 32.73 (SD 12.05) years; 29 males, 10 females, 11 white, 19 blacks, 8 Hispanic and 1 Asian], using the Mini International Neuropsychiatric interview version 5. Plasma total cholesterol was measured by High-performance liquid chromatography (HPLC) and psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) during hospitalization. We evaluated the relationship between Plasma total cholesterol and psychotic symptoms by calculating Pearson correlation coefficients between plasma cholesterol and PANSS positive, negative, general psychopathology and total scores.

**Results:** Plasma total cholesterol correlated negatively with PANSS positive subscale (r = -0.668, p = 0.006) but not with negative (r = 0.078, p = 0.730) and general psychopathology subscales (r = -0.011, p = 0.960) or with the total PANSS score (r = -0.202, p = 0.368).

**Conclusions:** Though cholesterol does not cross the blood brain barrier, it is important to investigate other potential mechanisms by which peripheral plasma cholesterol could influence brain cholesterol and ultimately 24S-hydroxycholesterol, a potent modulator of NMDARs. Elucidation of the underlying mechanisms of our observed association could lead to novel interventions for symptoms of schizophrenia.

**Keywords:** Schizophrenia, N-methyl-D-aspartate receptors, cholesterol, 24S-hydroxycholesterol

885. Striatal Functional Activation and Psychosis Risk

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**Background:** The striatum is involved in learning about motivationally relevant information, with distinct neural pathways differentially responsive to positive and negative outcomes and differentially affected by dopamine levels. Psychosis is strongly related to increased striatal dopamine. However, it is still unclear whether and how risk for psychosis is associated with task-related striatal dysfunction. If psychosis risk is associated with increased striatal dopamine, then it is expected that psychosis risk would be associated with (a) decreased striatal activation on a task involving learning from both positive and negative feedback (probabilistic category learning task; PCLT); and (b) increased striatal activation for unexpected reward, but decreased striatal activation for unexpected punishment on a task that separately assesses reward versus punishment feedback (reversal learning task; RLT).

**Methods:** Two groups of college student participants: (a) Psychosis Risk (n=21) with interview-rated attenuated psychotic symptoms; and (b) Controls (n=20). Participants completed both the PCLT & RLT during fMRI scanning.

**Results:** As expected there was decreased striatal activation on the PCLT in psychosis risk. Further, as expected, on the RLT, for unexpected reward psychosis risk was associated with increased striatal activation; but for unexpected punishment psychosis risk was associated with decreased striatal activation.

**Conclusions:** The current results suggest that psychosis risk is associated with a pattern of task-related neural dysfunction consistent with increased striatal dopamine in psychosis risk, specifically, increased activation in Direct/Go pathway and decreased activation in Indirect/NoGo pathway.

**Keywords:** attenuated psychotic symptoms, fMRI, striatum, Dopamine, Reward Learning
886. Can the General Cognitive Deficit in Psychosis Explain Small Working-Memory Capacity?

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Results: The storage capacity of working memory (k), measured via visual change-detection tasks, is smaller in patients with psychosis than controls. However, patients also experience a general cognitive deficit, and it is unclear whether small k is a primary source of dysfunction or a consequence of the general deficit. Here, we investigated whether performance on the Wechsler Abbreviated Scale of Intelligence (WASI), an established and reliable measure of general intellectual ability, could explain the commonly observed between-group difference in k.

Methods: Sixty-five patients with psychotic illnesses and 115 controls (aged 19–69 years) completed a visual change-detection task and the two-subtest form of the WASI. Bayesian hierarchical models were used to estimate k, and simultaneously estimate task and the two-subtest form of the WASI. Bayesian hierarchical models were used to estimate k, and simultaneously estimate the effects of various combinations of explanatory variables on k, from performance on the change-detection task. Explanatory variables included WASI full-scale IQ, T scores on the matrix-reasoning and vocabulary WASI subtests, and diagnostic group.

Results: Across all subjects, WASI performance explained some variance of k, which increased by about 0.8 per 15 points of IQ, on average. This relationship was driven by the matrix-reasoning subtest. Crucially, after controlling for WASI performance, k was estimated to be smaller by about 0.5 in patients than controls. Various Bayesian inferential techniques revealed that WASI performance was unable to fully capture the between-group difference in k.

Conclusions: The results are consistent with the suggestion that small k is a primary source of dysfunction in psychosis, which may constrain broader cognition, rather than a consequence of the general deficit.

Supported By: NIMH R01MH106324-01
Keywords: Schizophrenia, Working memory, Bayesian model, Computational Modeling

888. Cholinergic Neurotransmission and Cognition in Medication-Free Subjects with Psychosis

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Background: The cholinergic muscarinic system has been implicated in both psychosis and cognition. Here, we investigated in-vivo the cholinergic muscarinic system and its role in separate cognitive domains using a muscarinic M1 receptor antagonist as acute pharmacological challenge.

Methods: 33 medication-free subjects with a psychotic disorder (mean age 27 years) and 31 matched healthy controls (HC’s, mean age 25 years) underwent 1H-proton magnetic resonance spectroscopy (1H-MRS, PRESS) to measure choline concentrations in the anterior cingulate cortex (ACC) and striatum as well as cognitive assessment (CANTAB) twice: once after placebo and once after 4 mg biperiden (counterbalanced).

Results: No significant differences were found in both ACC and striatal choline levels between groups after placebo and M1 blockade did not significantly affect choline levels in both
regions. However, attention and striatal choline concentrations were significantly inversely correlated (p=0.025), in patients but not controls. Biperiden significantly worsened verbal (p<0.001 and p=0.032) and visual learning and memory (p=0.028) in patients and controls. No main or interaction effects were found for other cognitive domains.

**Conclusions:** This suggests a role for the cholinergic muscarinic system in cognition in psychosis and provides further in-vivo evidence that the M1 receptor is involved in cognitive functioning, particularly memory processes whereas attention may be mediated by nicotine receptors. Lack of differential effects of biperiden on choline concentrations and cognition between both groups could indicate that there were no severe cholinergic abnormalities present in our psychotic sample, although they might be present in chronic schizophrenia patients with more severe (cognitive) symptoms.

**Supported By:** NWO

**Keywords:** Muscarinic subtype 1 receptor, Cognitive Impairment, Psychotic disorder, 1H MRS

889. Bayesian Neural Adjustment of “the Need to Stop” Predicts Relapse in Methamphetamine-Dependent Individuals

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**Background:** Determining the precise nature of the cognitive dysfunctions in substance dependent individuals that contribute to relapse is essential for process-specific relapse prevention efforts. Recently, we have implemented a computational approach based on a Bayesian ‘ideal observer’ model to better delineate the cognitive dysfunctions associated with inhibitory function. This study investigates whether neural activation underlying those computational processes can predict the likelihood of relapse in recently sober methamphetamine-dependent individuals (MDI).

**Methods:** Fifty-eight MDI were recruited from a 28-day inpatient treatment program and completed a stop-signal task while undergoing functional magnetic resonance imaging (fMRI) after approximately 3-4 weeks of sobriety. These individuals were prospectively followed for 1 year and assessed for relapse to substance and alcohol use.

**Results:** Of the 58 MDI, 19 (33%) reported relapse one year after treatment. Cross-validated voxel-wise logistic regression analyses suggest that abnormalities in % signal change associated with Bayesian prediction errors (trial type - P(stop)) in the left inferior frontal gyrus (BA 47) and posterior cingulate (BA 31) predict relapse status (p<.01; Average Sensitivity=72%; Average Specificity=84%), where P(stop) is the model-inferred trial-wise expectation of encountering a stop signal. In contrast, neither clinical behavioral measures nor categorical task-related activations (e.g., stop error - stop success) survived cross-validation to predict relapse.

**Conclusions:** These results suggest that MDI exhibiting neural inefficiencies to support computational processes underlying inhibitory response prediction may be more likely to relapse. These computational markers may be superior to non-computational neural markers and other baseline behavioral measures to predict relapse in this population.

**Supported By:** P01-DA016663, P20-DA027834, R01-DA027797, and R01-DA018307

**Keywords:** Bayesian model, inhibitory control, methamphetamine dependence, stop-signal task, fMRI

890. Bipolar Disorder and Cannabis Use: A Survey of Substance Use Patterns

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UCSD

**Background:** The use of cannabis is highly prevalent in individuals with bipolar disorder (BD). Associations have been found between cannabis use and increased symptoms of psychosis. Further research delineating the use of cannabis versus other substances is needed among patients with affective disorders. This study examined the prevalence of current and prior use of cannabis, alcohol, stimulants, and nicotine among individuals with BD.

**Methods:** Phone interviews were administered to screen participants for studies on BD. Percentages of BD participants (N = 99) endorsing a history of or current use of cannabis, alcohol, nicotine and stimulants were calculated.

**Results:** Participants endorsed current (12%) and historical (64%) cannabis use. Over half (55%) reported more than 25 instances of lifetime cannabis use. The highest current substance use was found for nicotine (51%). Current alcohol use, history of stimulant use, and history of problematic alcohol use were endorsed by 11%, 43%, and 43% of participants, respectively. Percentages of participants with a history of using cannabis and alcohol, cannabis and stimulants, and alcohol and stimulants ranged from 25-34%.

**Conclusions:** High rates of cannabis use were found in individuals with BD. The rate of cannabis use was higher than the use of other substances except for nicotine, which has always been a legalized substance in the United States. Prospective treatment outcome studies are required measuring the patterns and effects of cannabis use in BD, therefore enabling clinicians to reach an evidence-based consensus to follow when informing patients of the effects of cannabis on specific psychiatric symptomatology.

**Supported By:** P50DA026306

**Keywords:** Bipolar Disorder, Cannabis, Smoking, Alcohol

891. El Viaje al Otro Lado: Relationship between Depression Onset in Latinas and Immigration Experience Coming to the US

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**Background:** Few studies investigate psycho-social hardships during immigrants’ travel. This retrospective pilot study asks if immigrant Latina women with clinically diagnosed depression experience greater trauma and hardship during...
their immigration travel than Latina immigrant women with no current psychiatric diagnosis.

**Methods:** 14 volunteers were assessed for trauma exposure, difficult life events, and depressive symptoms. 7 in experimental group had established depression diagnosis from FQHC. 7 recruited from community family centers as controls had no psychiatric diagnosis. Structured Clinician Interview for DSM III, Adverse Childhood Events Survey, and modified Life Events Difficulties Schedule were implemented. The Wilcoxon Rank Sum and Fisher's Exact were used for comparison.

**Results:** Control group reported increased challenge severity (p=.032). No significant difference found in trauma incidence (p=.26), childhood adversity (p=.5) or depressive symptoms in the first year following arrival to the US (p=.1). 71% of controls and 42% of experimental group traveled using human smuggler, aka “coyote”. Comparing modes of travel among groups, trauma exposure was increased in coyote travel (p=.031). Sleep deprivation (p=.01), intrusiveness (p=.008), and goal frustration (p=.048) were increased among coyote travelers. Coyote travel trended towards an increase in short term threat (p=.061).

**Conclusions:** With exception of perceived challenges, diagnosis of clinical depressive disorder did not significantly correlate with reported trauma or hardship. Of note, “coyote” travel among both groups significantly correlated with trauma exposure. No difference in depressive symptomatology one year after arrival suggest a high-risk adjustment period warranting a high-degree of clinical suspicion and screening in all newly immigrated patients.

**Supported By:** University of Arizona Tucson Department of Psychiatry

**Keywords:** Immigration, Adverse Childhood Experiences, Depression, Trauma, Latina

892. Evolution of Depression before, during and after a Major Social Movement

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**Background:** Social movements could have a profound impact on population mental health - yet their mental health consequences remain sparsely documented. We sought to examine the longitudinal patterns and predictors of depression trajectories before, during, and after the 2014 “Occupy Central/Umbrella Movement” (OCUM) in Hong Kong.

**Methods:** Prospective study of 1170 adults randomly sampled from the population-representative FAMLLY Cohort. We administered interviews at six time points from March 2009 to November 2015: twice each before, during, and after OCUM. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depressive symptoms and probable major depression (PHQ > 10). We investigated pre-event and time-varying predictors of depressive symptoms, including socio-demographics, general health status, resilience, family support, family harmony, and neighbourhood cohesion.

**Results:** Four trajectories were identified: “resistant” (22.6% of sample), “resilient” (37.0%), “mild depressive symptoms” (32.5%), and “persistent moderate depression” (8.0%). Baseline predictors that appeared to protect against “persistent moderate depression” included higher household income (OR 0.18, 95% CI 0.06-0.56), greater psychological resilience (OR 0.62, 95% CI 0.48-0.80), more family harmony (OR 0.68, 95% CI 0.54-0.86), higher family support (OR 0.80, 95% CI 0.69-0.92), better self-rated health (OR 0.30, 95% CI 0.17-0.55), and fewer depressive symptoms (OR 0.59, 95% CI 0.44-0.79).

**Conclusions:** Depression trajectories following a major protest were comparable to those in the wake of major population events. Health care professionals should be vigilant of the mental health consequences during and after social movements, particularly among individuals lacking social support.

**Supported By:** Jockey Club Charities Trust

**Keywords:** Depression, Longitudinal, Epidemiology, Trajectory, Social movement

893. Adverse Life Events, Psychiatric Comorbidity, and Biological Predictors of Postpartum Depression in an Ethnically Diverse Sample of Postpartum Women

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**Background:** Race, psychiatric history, and adverse life events have all been independently associated with postpartum depression (PPD). However, the role these play together in black and Latina women remains inadequately studied. Therefore, we performed a case-control study of PPD including comprehensive assessments of symptoms and biomarkers, while examining the effects of ancestry.

**Methods:** We recruited our sample (549 cases, 968 controls) at six weeks postpartum from clinics in North Carolina. PPD status was determined using the MINI-plus. Psychiatric history was extracted from medical records. Participants were administered self-report instruments to assess depression (Edinburgh Postnatal Depression Scale) and adverse life events. Levels of estradiol, progesterone, brain-derived neurotrophic factor (BDNF), oxytocin, and allopregnanolone were assayed. Principal components from genotype data were used to estimate genetic ancestry and logistic regression was used to identify predictors of case status.

**Results:** Results: This population was racially diverse (68% black, 13% Latina, and 18% European). PPD status was predicted by a history of major depression (p < 0.0001), history of anxiety...
894. Suicide Prediction Using Machine Learning Techniques in Screening and Clinician-Derived Data

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Background: Machine learning (ML) techniques are promising tools for prediction in psychiatry, as they are well suited to handle complex data sets with many correlated predictors. We sought to compare the performance of commonly used ML algorithms to predict suicide attempts using screening vs. clinician-derived data.

Methods: We utilized data from the Grady Trauma Project, which assesses trauma exposure in subjects seeking primary care from a large urban hospital. Subjects undergo a screening interview based on self-reported scales (socio-demographic data, PSS, CTQ, TEI, BDI) and selected subjects are invited to participate in a clinician-administered interview for DSM-IV diagnoses (SCID/MINI). Subjects were split into balanced training (N=814, 80%) and testing (N=203, 20%) sets, each of which had 16% suicide attempters. Suicide risk factors were entered into support vector machines (SVM) and least absolute shrinkage and selection operator (LASSO) models with 100 iterations in which each iteration included all attempters and an equal number of non-attempters.

Results: Self-reported screening data (PSS, CTQ, TEI, employment, psychiatric hospitalization) provided reasonable sensitivity (64%) and specificity (76%; AUC 70%). Areas Under the Curve (AUC) did not differ when clinician-derived data (major depressive disorder and any psychotic disorder) was available for selection. The LASSO (AUC 70%) and SVM (AUC 71%) models did not differ substantially in accuracy.

Conclusions: We describe a ML-derived algorithm for suicide prediction and suggest risk factors that are most relevant for prediction. In this cohort, the addition of clinician-obtained data did not improve prediction accuracy over self-reported screening data.

Supported By: R25

Keywords: Suicide risk factors, Machine learning, Precision psychiatry, Screening vs. clinician-administered instruments, Urban population sample

895. Neuroleptic Malignant Syndrome Diagnosis Risk is Greatest in Young Adult Men

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Background: Sex and age are suspected but unproven risk factors for neuroleptic malignant syndrome (NMS), a potentially fatal adverse drug reaction associated with antipsychotic medications. This study determined the sex ratio of NMS cases identified by a systematic review of the world literature in order to estimate the relative risk for men and women of being diagnosed with NMS. The sex-specific age distribution of NMS was also examined.

Methods: EMBASE and PubMed databases were searched using unrestricted criteria to identify all published observations of NMS. Any accessible and interpretable report published between 1986 and 2014 was eligible for inclusion. Primary sources were given preference over secondary sources (e.g., reviews). Relevant reports and cases in which an NMS diagnosis was less likely were excluded. The sex distributions observed in studies and large (n>10) case series were treated as independent estimates; single case reports and small case series (i.e., n<11) were combined into a single series for the purpose of computing a single sex ratio for the aggregate sample. Standard graphical analysis and measures of association were used to examine sex ratio and age distributions.

Results: Most (75%) of the 28 sex ratio estimates showed male preponderance (median sex ratio 1.47, 95% CI 1.20-1.80). NMS frequency was highest in the 20-25 years age group, and declined progressively with advancing age; males outnumbered females at all ages. These results are limited by heterogeneity of case ascertainment procedures and potential publication bias.

Conclusions: Young adult men appear to be at greatest risk for NMS.

Keywords: neuroleptic malignant syndrome, Gender differences, Risk factor, Age

896. Genetic and Phenotypic Overlap of Specific Obsessive-Compulsive Subtypes with Tourette Syndrome

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Supported By: R01, T32

Keywords: Postpartum Depression, psychiatric comorbidities, Ancestry, Sex-steroid hormones, Trauma Exposure

Supported By:

Results:

Methods:

Keywords: Neuroleptic Malignant Syndrome, Gender differences, Risk factor, Age

Conclusions:

Supported By:

Keywords: Postpartum Depression, psychiatric comorbidities, Ancestry, Sex-steroid hormones, Trauma Exposure

Supported By:
Background: The unique phenotypic and genetic aspects of obsessive-compulsive (OCD) and attention-deficit/hyperactivity disorder (ADHD) among individuals with Tourette syndrome (TS) have not been well characterized.

Methods: OCD and ADHD symptom patterns were identified among patients with TS and their family members ($N=3494$) using exploratory factor and latent class analyses; clinical associations and heritability of these factors were examined.

Results: Factor analyses yielded 2- and 8-factor models for ADHD and OCD, respectively. Both ADHD factors (inattention and hyperactivity/impulsiveness) were genetically related to TS, ADHD, and OCD; all OCD factors (related to symmetry/contamination, unusual thoughts, aggressive urges, and hoarding) were genetically related to OCD. The OCD aggressive urges factor was genetically associated with TS and ADHD, the symmetry/exactness and fear of harm factors were associated with TS, and the hoarding factor was associated with ADHD. Latent classes based on OCD and ADHD factor sum scores to examine the relationships between OCD and ADHD symptoms in probands and family members revealed a three-class solution: ADHD; TS, ADHD, and OCD; all OCD factors (related to symmetry/exactness, aggressive urges, and hoarding) were genetically related to OCD. The OCD aggressive urges factor was genetically associated with TS and ADHD, the symmetry/exactness and fear of harm factors were associated with TS, and the hoarding factor was associated with ADHD. Latent classes based on OCD and ADHD factor sum scores to examine the relationships between OCD and ADHD symptoms in probands and family members revealed a three-class solution: ADHD; OCD+ADHD; and asymmetry/exactness, hoarding, and ADHD. The majority of participants with TS, ADHD, mood, and anxiety disorders, as well as mothers, fathers, and probands, were classified in the ADHD class. In contrast, the largest percentage of participants with OCD and disruptive behavior disorders were classified in the asymmetry/exactness, hoarding, and ADHD class.

Conclusions: Symmetry/exactness, aggressive urges, fear of harm, and hoarding show complex genetic relationships with TS, OCD, and ADHD, and transcend diagnostic boundaries, perhaps representing a failure of top-down cognitive control common to all three disorders.

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Keywords: Tourette's Syndrome, Obsessive Compulsive Disorder (OCD), ADHD, Heritability, Endophenotypes
**Background:** Religiosity has been linked to outcome in medical illness. The current study examined the potential relationship between religiosity and demographic and clinical variables in psychiatric inpatients.

**Methods:** 688 adults admitted to an acute psychiatric facility with a primary Mood or Psychotic Disorder completed the Duke University Religion Index (DUREL). The DUREL measures religious activity in 3 domains: organized religious activities (ORA), non-organized religious activities (NORA), and internal religiosity (IR). Univariate analysis was performed to explore the distribution of variables and identify outliers. Bivariate analysis with Chi-square and t-tests were used to examine the association between the DUREL subscales and demographic, clinical, and outcome measures.

**Results:** Elevated religious activity was common in the inpatient sample with 58% categorized as high IR, 43% high NORA and 36% high ORA. Psychotic disorders were more likely to be present in the inpatients scoring high on each DUREL subscale: IR (68% vs. 32%, p < 0.01), NORA (68% vs. 32%, p < 0.05), and ORA (70% vs. 30%, p < 0.05). High ORA scores were also associated with an increased length of stay (mean days +SD, 9.1 ± 0.4 vs. 8.2 ± 0.25, p < 0.05). Female were more likely than male inpatients to score high on the ORA (p < 0.05), NORA (p < 0.05), and IR (p < 0.0001) subscales. There was also a significant relationship detected between age and high IR scores (p < 0.005).

**Conclusions:** While preliminary, these results suggest that a brief measure of religiosity can provide some important information concerning clinical features and acute outcome in patients hospitalized with serious mental illness.

**Keywords:** demographic factors, Psychotic Disorders, Clinical, Rating scales

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**899. Body Mass Index is Correlated with C-Reactive Protein in Patients with Schizophrenia**

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**Background:** Schizophrenia has been associated with increased body mass index (BMI). Evidence also suggests that C-reactive protein (CRP), an acute-phase plasma protein, is elevated in patients with schizophrenia. CRP levels have been correlated with BMI among individuals without schizophrenia but there is a paucity of studies evaluating the association of BMI with CRP in individuals with schizophrenia. Thus, we examined the association of BMI and plasma CRP levels in a sample of patients with schizophrenia.

**Methods:** Our sample consisted of 39 patients with schizophrenia (diagnosed with the Mini International Neuropsychiatric Interview version 5.0). Fasting blood was collected from all the patients and plasma CRP measured using ELISA. BMI was calculated for each patient. The distribution of CRP was right-skewed and logarithmic transformation was done to normalize the data. 4 patients had missing data. We carried out Pearson correlational analysis to assess the association between BMI and logCRP and partial correlation analyses to control for potential confounders.

**Results:** BMI positively correlated with logCRP (r = 0.387, p = 0.022) and this finding persisted after controlling for age, sex, race and education.

**Conclusions:** Elevated BMI might contribute to increased inflammation in patients with schizophrenia. Since elevated inflammation has been associated with negative outcomes such as worsening cognition, cardiovascular complications and accelerated aging, the findings of this study provide further justification for supporting the evaluation of interventions targeted at reducing BMI in patients with schizophrenia.

**Keywords:** BMI, C-reactive protein, Schizophrenia, Inflammation

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**900. The Impact of Substance Use Disorders Late in Life**

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**Background:** Substance use disorders (SUD) have been proven a particularly severe health problem in United States, with estimates of up to 5.7 million affected older individuals by 2020.

**Methods:** We examined SUD in 7,264 older individuals (age>50 years) admitted to Harris County Psychiatric Center between January 2010 and September 2016 and the impact of SUD as a predictor of clinical outcomes (hospitalization length of stay (LOS), number of psychiatric and medical comorbidities). SUD status (binary (+/-) categorical variable) was based on urine drug screen (UDS) and/or discharge diagnosis of SUD and categorized by type.

**Results:** SUD+ was found in 1,895 subjects (26.09%). Cocaine was the leading substance of misuse (N=692/9.53%), followed by opiates (N=274/3.77%), cannabinoids (N=254/3.5%), and alcohol (N=218/3.0%). SUD+ for one substance was observed in 1,326 subjects (18.28%), while 560 individuals (7.72%) were positive for two or more substances. SUD status (+/-) was predicted by longer LOS and increased number of psychiatric comorbidities (p<0.03 and p < .001 respectively). The total number of medical comorbidities was predicted by SUD type, specifically barbiturates, opiates, and alcohol (p < .01).

**Conclusions:** In our study, 26.09% of subjects were diagnosed with SUD. These rates exceed community
901. Abnormal Sleep Duration Associated with Hastened Depressive Recurrence in Bipolar Disorder

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Background: Abnormal sleep duration (ASD, < 6 or ≥ 9 hours) is common in bipolar disorder (BD), and often persists beyond acute mood episodes. Few longitudinal studies have examined the ASD’s impact upon BD illness course. The current study examined the longitudinal impact of ASD upon bipolar depressive recurrence/recovery.

Methods: Outpatients referred to the Stanford BD Clinic during 2000-2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation at baseline, and with the Clinical Monitoring Form at monthly follow-ups for up to two years of naturalistic treatment. Prevalence and clinical correlates of ASD in recovered ( euthymic ≥ 8 weeks) and depressed BD patients were assessed. Kaplan-Meier analyses (Log-Rank tests) assessed relationships between baseline ASD and longitudinal depressive severity, with Cox Proportional Hazard analyses assessing potential mediators.

Results: ASD was only half as common among recovered versus depressed BD outpatients, but was significantly associated with hastened depressive recurrence (Log-Rank p = 0.007), mediated by lifetime anxiety disorder and attenuated by lifetime history of psychosis, and had only a non-significant tendency towards association with delayed depressive recovery (Log-Rank p = 0.07). In both recovered and depressed BD outpatients, baseline ASD did not have significant association with any baseline BD illness characteristic.

Conclusions: Baseline ASD among recovered BD patients may be a risk marker for hastened depressive recurrence, suggesting it could be an important therapeutic target between mood episodes.

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Keywords: Bipolar Disorder, Sleep, Bipolar Depression, Recurrence

902. Symptom Network Structure as a Predictor of Comorbid Alcohol Use Disorder among Individuals with an Internalizing Disorder

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Background: We previously used a network approach to show that drinking to cope (DTC) is a central factor in maintaining the connectivity of internalizing (INT) disorders and comorbid alcohol use disorder (AUD) in AUD inpatients. Here, we extend that work in a prospective nationally representative community sample (NESARC).

Methods: Networks were constructed from Wave 1 data from participants who had at least one INT disorder and no AUD in the past year and were sub-grouped according to whether AUD remained absent (N=1,401) or had newly onset (N=314) by Wave 2. A separate set of networks were based on respondents who had at least one INT disorder and AUD at Wave 1 that then either persisted (N=285) or remitted (N=314) by Wave 2.

Results: The group who developed a new AUD onset at Wave 2 had higher network density and larger mean centrality for DTC (Cohen d = 1.65) at Wave 1 compared to the group in which AUD remained absent at both waves. The group whose AUD persisted between both waves had higher network density and larger mean centrality of panic, generalized anxiety, and depression (Cohen d = 0.52, 0.65, and 1.15, respectively) at Wave 1 compared to the group in which AUD remitted between Waves 1 and 2.

Conclusions: This study demonstrates baseline network structure is predictive of the prospective course of comorbid AUD among individuals with INT disorders and that DTC plays a central role in AUD onset while INT symptom load plays a more important role in AUD persistence.

Supported By: R01-AA015069; T32DA037183

Keywords: Network Analysis, Comorbidity, Alcohol Use Disorder, Internalizing Disorders, Clinical High Risk Predictors

Conclusions: Baseline ASD among recovered BD patients may be a risk marker for hastened depressive recurrence, suggesting it could be an important therapeutic target between mood episodes.

903. Serotonin Transporter Relationships with Treatment Response to Meditation Interventions for PTSD

Jeffrey Bishop1, Paul Thuras2, Adam Lee3, Doris Clancy4, Christopher Erbes5, Melissa Polusny5, Gregory Lamberty5, and Kelvin Lim6

1University of Minnesota, 2Minneapolis Veterans Affairs Health Care System, 3University of Minnesota College of Pharmacy, Department of Experimental and Clinical Pharmacology, 4University of Minnesota Medical School, Department of Psychiatry, 5University of Minnesota Medical School, Department of Psychiatry, Minneapolis Veterans Affairs Health Care System, 6University of Minnesota

Results: ASD was only half as common among recovered versus depressed BD outpatients, but was significantly associated with hastened depressive recurrence (Log-Rank p = 0.007), mediated by lifetime anxiety disorder and attenuated by lifetime history of psychosis, and had only a non-significant tendency towards association with delayed depressive recovery (Log-Rank p = 0.07). In both recovered and depressed BD outpatients, baseline ASD did not have significant association with any baseline BD illness characteristic.

Conclusions: Baseline ASD among recovered BD patients may be a risk marker for hastened depressive recurrence, suggesting it could be an important therapeutic target between mood episodes.

Supported By: Pearseirnt Family Foundation, the Mitchell Foundation, and the Holland Foundation. Preparation of this report was supported by a National Institute of Mental Health Research Scientist Development Award (K01MH100433) to A. Gershon. The funding sources had no role in the study’s design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the article for publication.

Keywords: Bipolar Disorder, Sleep, Bipolar Depression, Recurrence

902. Symptom Network Structure as a Predictor of Comorbid Alcohol Use Disorder among Individuals with an Internalizing Disorder

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Background: We previously used a network approach to show that drinking to cope (DTC) is a central factor in maintaining the connectivity of internalizing (INT) disorders and comorbid alcohol use disorder (AUD) in AUD inpatients. Here, we extend that work in a prospective nationally representative community sample (NESARC).

Methods: Networks were constructed from Wave 1 data from participants who had at least one INT disorder and no AUD in the past year and were sub-grouped according to whether AUD remained absent (N=1,401) or had newly onset (N=314) by Wave 2. A separate set of networks were based on respondents who had at least one INT disorder and AUD at Wave 1 that then either persisted (N=285) or remitted (N=314) by Wave 2.

Results: The group who developed a new AUD onset at Wave 2 had higher network density and larger mean centrality for DTC (Cohen d = 1.65) at Wave 1 compared to the group in which AUD remained absent at both waves. The group whose AUD persisted between both waves had higher network density and larger mean centrality of panic, generalized anxiety, and depression (Cohen d = 0.52, 0.65, and 1.15, respectively) at Wave 1 compared to the group in which AUD remitted between Waves 1 and 2.

Conclusions: This study demonstrates baseline network structure is predictive of the prospective course of comorbid AUD among individuals with INT disorders and that DTC plays a central role in AUD onset while INT symptom load plays a more important role in AUD persistence.

Supported By: R01-AA015069; T32DA037183

Keywords: Network Analysis, Comorbidity, Alcohol Use Disorder, Internalizing Disorders, Clinical High Risk Predictors

903. Serotonin Transporter Relationships with Treatment Response to Meditation Interventions for PTSD

Jeffrey Bishop1, Paul Thuras2, Adam Lee3, Doris Clancy4, Christopher Erbes5, Melissa Polusny5, Gregory Lamberty5, and Kelvin Lim6

1University of Minnesota, 2Minneapolis Veterans Affairs Health Care System, 3University of Minnesota College of Pharmacy, Department of Experimental and Clinical Pharmacology, 4University of Minnesota Medical School, Department of Psychiatry, 5University of Minnesota Medical School, Department of Psychiatry, Minneapolis Veterans Affairs Health Care System, 6University of Minnesota
Saturday Abstracts

904. DNA Methylation Associated with PTSD and Depression in World Trade Center Responders: An Epigenome-Wide Study

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Background: Although differential methylation patterns are thought to be associated with posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), findings from previous epigenome-wide association studies (EWAS) have been inconsistent, possibly due to small sample sizes, measurement differences, and failure to account for comorbid PTSD/MDD. The current EWAS of 473 World Trade Center (WTC) responders investigated DNA methylation patterns associated with PTSD and MDD separately as well as jointly.

Methods: Methylation was profiled on blood samples using Illumina 450K Beadchip. EWAS analyses compared current versus never PTSD, current versus never MDD and current versus never comorbid PTSD/MDD, adjusting for cell types and demographic confounders. Pathway and gene set enrichment analyses were also performed to understand the complex biological systems of PTSD and MDD.

Results: No significant genome-wide associations were found. However, cg06182923 located in the gene body of CSMD2 was differentially methylated at nominal p<0.001. Serine type endopeptidase, endoplasmic reticulum, adaptive immune system, E2F pathway and N-linked glycosylation were identified among the top ranking gene sets.

Conclusions: The current EWAS analysis was the largest study to date, and the failure to detect significant genome-wide associations constitutes an important non-replication of disparate findings from previous, smaller EWAS and candidate gene studies of PTSD and MDD. Future studies are needed to test whether CSMD2 is a potential novel epigenetic marker for comorbid PTSD and depression. Enriched gene sets involved in several biological pathways, including stress response, were identified, supporting that multiple genes work in concert to regulate these complex phenotypes.

Supported By: VA grant 5I01CX000683-01
Keywords: PTSD, Mindfulness Meditation, Serotonin Transporter Gene

905. Genetic Variants in the Circadian Rhythm Pathway Predict PTSD Symptoms following Trauma Exposure

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Background: Genetic variants in circadian rhythm (CR) genes have been associated with vulnerability to PTSD and related neuropsychiatric disorders. In this study, we assessed whether previously identified CR variants predict PTSD severity following motor vehicle collision (MVC) and major thermal burn injury (MThBI), and whether such influence is stress severity- or sex-dependent.

Methods: Prospective studies of PTSD development following MVC (n=907) and MThBI (n=68) served as discovery and replication cohorts, respectively. In both cohorts, individuals were enrolled and DNA samples collected in the immediate aftermath of trauma, and PTSD symptom severity was assessed using validated questionnaires. Repeated measure mixed
modeling adjusted for age, sex, study site, and time following trauma were used to evaluate associations between PTSD severity over time and 31 common genetic variants across nine CR-pathway genes (PER3, NPAS2, PER2, CLOCK, RORB, BMAL1, TIMELESS, RORA, and TEF). Potential SNP*stress and SNP*sex interactions were also evaluated.

**Results:** Five SNPs from four CR-associated genes predicted PTSD outcomes following MVC (False Discovery Rate < 5%): BMAL1 (rs969485, p = 6.12x10^{-4}); RORA (rs4775351, p = 4.79x10^{-4}); NPAS2 (rs12622050, p = 5.61x10^{-4}); TEF (rs758324, p = 6.47x10^{-5}); TEF (rs738499, p = 1.38x10^{-3}). Of note, TEF polymorphism rs738499 also predicted PTSD severity in a FKBP5 vulnerability allele-dependent manner (rs738499*FKBP5 rs3800373, p = 2.92x10^{-5}). Stress-dependent associations for TEF alleles rs738499 and rs738499 replicated in the MThBI cohort (p = 2.89x10^{-4}, p = 0.043, respectively).

**Conclusions:** The results of our study suggest that genetic variants involved in CR pathway signaling, particularly in the TEF gene, predict PTSD severity after MVC and MThBI in a stress-dependent manner.

**Supported By:** R01 AR060852

**Keywords:** Circadian Rhythms, PTSD - Posttraumatic Stress Disorder, Genetic epidemiology, Trauma Exposure, Stress

### 906. Genome-Wide DNA Methylation Analysis of FACS Sorted Live Human Brain Compared to Buccal, Saliva, and Blood from Same Individuals

Benjamin Hing¹, Patricia Braun¹, Yasunori Nagahama², Lindsey Gaul¹, Jonathan Heinzman¹, Melissa McKane¹, Andrew Grossbach², Brian Dlouhy², Matthew Howard², Hiroto Kawasaki², Brian Dlouhy², Matthew Howard², and Gen Shinozaki¹

**Background:** Differential DNA methylation (DNAm) in the brain is associated with a number of psychiatric diseases, but access to brain tissues is essentially limited to post-mortem samples. The use of surrogate tissues has become common in identifying methylation changes associated with psychiatric disease. In this study, we determined the extent to which these peripheral tissues can be used as surrogates for assessing DNAm in the brain.

**Methods:** DNA from blood, saliva, buccal, and live brain tissue samples from 13 treatment refractory epilepsy patients undergoing brain resection were collected. Fluorescence activated cell sorting was performed on a subset of brains and resulted in seven non-neuronal and two neuronal cell populations. Genome-wide DNAm was assessed with the Infinium HumanMethylationEPIC BeadChip array. Data were processed and analyzed with the R package RnBeads.

**Results:** Non-neuronal cell populations were more highly correlated than were neuronal populations to saliva (r² = 0.78 vs. 0.66), blood (r² = 0.68 vs. 0.60), and buccal samples (r² = 0.74 vs. 0.64). Unsorted brain tissue showed saliva-brain correlation (r² = 0.79) was higher than that for blood-brain (r² = 0.74) and buccal-brain (r² = 0.71). Genomic region comparisons showed that correlations within promoter (saliva r² = 0.88, blood r² = 0.84, buccal r² = 0.83) and genic regions (saliva r² = 0.82, blood r² = 0.77, buccal r² = 0.75) were higher than within intergenic regions (saliva r² = 0.67, blood r² = 0.60, buccal r² = 0.55).

**Conclusions:** Genome-wide analysis of DNAm from saliva, buccal, and blood tissues all revealed a high degree of correlation with live brain DNAm within individuals, but saliva was most highly correlated. This indicates that saliva is the most useful surrogate for assessing DNAm in the brain.

**Keywords:** Epigenetics, Surrogate tissue, Brain, DNA methylation, EWAS

**Background:** Exposure to “early life adversity” (e.g., in the first two decades of life) is known to predict DNA methylation (DNAm). However, few studies have investigated whether adversity has time-dependent effects, varying based on the age at exposure.

**Methods:** Using an innovative two-stage structured lifecourse modeling approach (SLCMA), we tested the central hypothesis that there are sensitive periods associated with DNAm, or life stages when adversity induced greater DNAm changes. We tested this sensitive period hypothesis in relation to two alternative explanations: an accumulation hypothesis, in which the effect of adversity on DNAm increases with the number of occasions exposed, regardless of timing, and a recency model, in which the effect of adversity on DNAm is stronger for more proximal events. Data for our prospective study came from the Accessible Resource for Integrated Epigenomics Studies (ARIES), a subsample of 1,018 mother-child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC).

**Results:** After covariate and cell-type adjustment and Bonferroni correction for multiple testing, we identified 40 CpG sites that were differentially methylated following exposure to adversity. Nearly all of these loci (n = 38) were related to adversity exposure in infancy. Financial stress, maternal psychopathology, and neighborhood disadvantage were the three types of adversities predicting the greatest number of epigenome-wide DNAm changes.

**Conclusions:** These results suggest that the developmental timing of adversity explains more variability in DNA methylation than the accumulation or recency of exposure. Infancy appears to be a sensitive period when exposure to adversity predicts differential DNA methylation patterns.

**Supported By:** Harvard Catalyst

**Keywords:** Epigenetics, Adverse Childhood Experiences, sensitive period, DNA methylation, children
908. Genome-Wide Association Study Identifies HTR2B as a Risk Variant of Cannabis-Related Aggression in African Americans

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Background: Research is needed to elucidate the clinical consequences of the increasing legalization and use of marijuana. Recent studies have shown that cannabis use is associated with greater risk of violent and antisocial behavior. However, no studies to date have examined the genetic predictors of aggressive behavior following cannabis use. The purpose of this study is to identify genetic variants associated with cannabis-related aggressive behavior in African American (AA) and European American (EA) populations.

Methods: Our sample included the Yale-Penn 1 sample (2,185 AAs and 1,362 EAs), augmented by additional identically ascertained subjects (1,084 AAs and 1,184 EAs, Yale-Penn 2 sample). All subjects were cannabis-exposed. Cannabis-related aggression was assessed using the following interview item: “Did you ever get into physical fights while using marijuana?”

Results: On meta-analysis (3269 AAs, 2546 EAs), we identified two genome-wide significant (GWS) risk loci in AAs, but none in EAs. These included rs35750632 (β=0.54, P=1.79 × 10-8) in the proteasome 26S subunit, non-ATPase 1 gene (PSMD1), and rs17440378 (β=0.57, P=2.16 × 10-8) in the serotonin receptor 2B (HTR2B). HTR2B was previously found in or near NPSR1, ESR1, GABRA6, PER3, NR3C2, and DRD4. Chronic stressors were more influential than single, severe, life events.

Conclusions: Our findings implicating HRT2B and PSMD1 in an AA population are first genetic loci associated with cannabis-related aggression.

Supported By: NIMH 5T32MH014276-41

Keywords: GWAS, Cannabis, Aggression, African-American, European population

909. Predicting Attention-Deficit/hyperactivity Disorder Severity from Stress and Stress Response Genes

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Background: Identifying genetic variants contributing to attention-deficit/hyperactivity disorder (ADHD) is complicated by the involvement of numerous common genetic variants with small effects, interacting with each other as well as with environmental factors, such as stress exposure. Random forest regression is well-suited to explore this complexity, as it allows for the analysis of many predictors simultaneously, taking into account any higher-order interactions among them.

Methods: Using random forest regression, we predicted ADHD severity, measured by Conners’ Parent Rating Scales, from 686 adolescents and young adults (including 281 diagnosed with ADHD). The analysis included 17,374 single nucleotide polymorphisms (SNPs) across 29 genes previously linked to hypothalamic-pituitary-adrenal (HPA) axis activity, together with information on exposure to 24 individual long-term difficulties or stressful life events.

Results: The model explained 12.5% of variance in ADHD severity. The most important SNP for prediction, which also showed the strongest interaction with stress exposure, was located in a region regulating the expression of telomerase reverse transcriptase (TERT). Other high-ranking SNPs were found in or near NPSR1, ESR1, GABRA6, PER3, NR3C2, and DRD4. Chronic stressors were more influential than single, severe, life events.

Conclusions: Random forest regression may be used to investigate how multiple genetic and environmental factors jointly contribute to ADHD. It is able to implicate novel SNPs of interest, interacting with stress exposure, and may explain inconsistent findings in ADHD genetics. This exploratory approach may be best combined with more hypothesis-driven research; top predictors, and their interactions with one another, should be replicated in independent samples.

Supported By: NIH, NWO, European Community’s Seventh Framework Programme, European Community’s Horizon 2020 Programme

Keywords: HPA axis, Genetics, Psychosocial Stress, Attention Deficit Hyperactivity Disorder, Gene-environment interaction

910. Accelerated Epigenetic Aging in Patients with Bipolar Disorder and Their Siblings

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1The University of Texas Health Science Center at Houston, 2Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences,
Background: First-degree relatives of patients with bipolar disorder (BD) are at increased risk for developing BD compared to controls. Based on evidence that DNA methylation might underlie this risk, we aimed to investigate whether siblings would share common alterations in peripheral DNA methylation markers with BD patients. In addition, considering the reported accelerated aging and cellular senescence in mood disorders, we aimed to compare DNA methylation age acceleration in these subjects.

Methods: Twenty two patients with BD-I, 16 siblings, and 20 age- and sex-matched healthy controls were enrolled for this preliminary study. Peripheral blood DNA methylation levels were interrogated by the Infinium HumanMethylation450 BeadChip and analyzed with the RnBeads R package using hierarchical linear models. DNA methylation age and accelerated aging were calculated based on the methylation levels of 353 CpGs using an online calculator.

Results: No locus withstood correction for multiple testing (FDR adjusted p<.05). However, patients and controls showed nominally significant differences in 422 probes, while siblings and controls differed for 538 probes (unadjusted p<.05). Annotated genes that were concordant between the lists of nominally differentially methylated genes between controls vs. patients and controls vs. siblings (“risk genes”) were enriched for pathways related to glutathione redox reactions, glutathione-mediated detoxification, among others. In addition, epigenetic aging among older subjects showed a greater acceleration in patients (p=.004) and siblings (p=.018) compared to controls.

Conclusions: Our preliminary results suggest that BD patients and their siblings show an accelerated epigenetic aging possibly associated with the DNA methylation-based modulation of the glutathione metabolism.

Supported By: R01MH085667; Pat Rutherford, Jr. Endowed Chair in Psychiatry; John S. Dunn Foundation from United States

Keywords: Bipolar Disorder, High Risk, DNA methylation, Epigenetics, Aging

911. Gene-By-Environment Analyses Reveal Obstetric Complications Interact with Genetics to Influence Psychopathology and Personality

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University of Edinburgh

Background: Accumulating evidence suggests obstetric complications (OCs) impact future health and they have been implicated in the aetiology of psychiatric disorders. OCs are hypothesised to interact with underlying genetics to increase risk. We undertook a genome-wide search of interactions with OCs for a variety of outcomes in the Generation Scotland cohort.

Methods: We performed a series of single-SNP genome-wide environment interaction studies using a linear regression model with age, gender and 20 principal components as covariates of no interest. We investigated measures of psychopathology (General Heath Questionnaire; GHQ-28, Schizotypal Personality Questionnaire; SPQ, Mood Disorder Questionnaire; MDQ) and personality (Eysenck Extraversion & Neuroticism) as outcomes with the following obstetric variables: birth-weight, labour induction, c-section, use of forceps, gestational age and neonatal care admission. All p-values are Bonferroni-corrected.

Results: Genome-wide significant gene-environment interactions were observed for the GHQ with neonatal care admission (N=1566; top SNP rs17141144; p=6.71x10^-7; LOC107986773; intronic), forceps (N=1701; top SNP rs17065704; p=3.24x10^-6; PEX7; intronic) and birth-weight (N=2459; top SNP rs9608151; p=0.02; intergenic). Significant interactions were also found for the SPQ-Total with neonatal care admission (N=944; rs1251224; p=0.02; intergenic) and birth-weight (N=1558; rs7803908, p=0.005; TNS3; intronic), for SPQ-Interpersonal with birth-weight (rs822038; p=0.03; AHCYL2; intronic) and for Eysenck Extraversion with birth-weight (N=2674; top SNP rs7137811; p=0.007; intergenic) and gestational age (N=1563; rs17708877; p=0.01; DGKB; intronic).

Conclusions: This is, to our knowledge, the first genome-wide study to reveal gene-by-environment interactions with OCs impact a wide variety of psychological traits. Genes implicated include PEX7, involved in neuronal migration, and DGKB, linked to cognition and possibly schizophrenia.

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Keywords: obstetric complications, Gene-environment interaction, psychological distress, Schizotypy, extraversion

912. The Relationship between Inflammatory Genes and Cognitive Flexibility among Adolescents with Bipolar Disorder

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Background: Inflammation is a leading candidate biomarker in bipolar disorder (BD). Findings suggest inflammatory genes may play a key role underlying neurostructural and neuropathological aberrancies in BD. The question therefore arises as to whether inflammatory genes are pertinent to neurocognitive deficits in BD.

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We examined the effects of interleukin (IL)-1Beta genetic variability on cognitive flexibility in BD adolescents. Secondary analyses focused on the effects of a composite variable, comprising IL-1Beta and three other inflammation-related single nucleotide polymorphisms, on cognitive flexibility in BD adolescents.

**Methods:** Subjects were 42 with BD and 54 healthy controls (HC), 13-20 years old. The following were genotyped using standard LifeTechnologies TaqMan® procedures on the Applied Biosystems 7500 Sequence Detection: IL-1Beta rs16944, IL-6 rs1800795, IL-10 rs1800896, and tumor necrosis factor alpha rs1800629. Saliva was collected using DNA Genotek Oragene®-500 kits. Cognitive flexibility was assessed via the intra/ extradimensional shift (IED) task (Cambridge Neuropsychological Tests Automated Battery subtest).

**Results:** Within BD adolescents, IL-1Beta risk allele (A) carriers completed more stages of the IED task than non-carriers (U= 291.50, p=0.004). Moreover, a significant positive correlation was found between number of risk inflammation-related alleles and reduced errors on the extra-dimensional stage of the IED task in BD adolescents (rs= 0.362, p=0.020). No significant genetic-related differences were seen within HCs.

**Conclusions:** Findings suggest that inflammation-related genes are relevant to cognitive flexibility deficits among BD adolescents, but not among HCs. Future studies are warranted to examine whether similar findings are observed for other neurocognitive tasks, and whether present findings are mediated by serum levels of inflammatory proteins.

**Supported By:** NARSAD

**Keywords:** Genetics, Bipolar Disorder, Adolescence, Neurocognition, Inflammation

913. Association between GLP1 Receptor Gene Polymorphisms and Reward Learning across Psychiatric Diagnoses

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**Background:** Glucagon-like peptide 1 receptors (GLP-1R) are widely expressed in the brain. Evidence suggests that they may have a role in reward processing and neuroprotection. However, the association of GLP-1R with anhedonia and severity of mood and anxiety symptoms has not been studied in humans. In this study, we examined the association of GLP-1R polymorphisms with psychiatric symptoms, as well as subjective and laboratory-based measures of anhedonia.

**Methods:** Clinical scales (SHAPS, MASQ, MADRS, PANSS Positive and PANSS Negative), reward learning (as assessed using a probabilistic reward task, PRT), and DNA samples were collected in 100 controls and 164 patients with a diagnosis of schizophrenia spectrum or mood disorder. Based on a systematic review, 9 SNPs in the GLP-1R gene were selected for an association analysis. Associations of each GLP-1R polymorphism with anhedonia and response bias in the PRT (i.e., the preference for a more frequently rewarded stimulus) were analyzed using a linear regression model, controlling for clinical or sociodemographic variables.

**Results:** SHAPS score was significantly different between patients and controls and SNPs in GLP-1R did not have a significant effect on this difference. A allele in rs10305492 (p<0.007), G allele in rs1042044 (p<0.01) and A allele in rs6923761 (p<0.048) were significantly correlated with response bias when controlling for age, sex or case-control status. Only rs10305492 (p<0.007), rs1042044 (p<0.01) were significant when the results were corrected for total scores of MADRS, YMRS, PANSS positive and negative scales and GQAS and AAS subscores of MASQ.

**Conclusions:** Our findings suggest a possible correlation with rs10305492 with anhedonia.

**Supported By:** NIMH R03

**Keywords:** GLP1 receptor, anhedonia, SHAPS, PRT, response bias

914. Toxoplasma Gondii Serointensity and Seropositivity and Their Heritability and Household-Related Associations in the Old Order Amish

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**Background:** Toxoplasma gondii is an intracellular parasite, infecting one-third of the world’s population. Exposure via food and non-food related factors (i.e., contact with cat feces) is required for infection, however, host genetic factors may play a role in susceptibility. Latent T. gondii infection has been consistently associated with mental illness, including...
schizophrenia, bipolar disorder, suicidal behavior and its endophenotypes impulsivity and aggression, and less consistently associated with depression.

**Methods:** Toxoplasma gondii (T. gondii) IgG antibody titers were measured in 2017 Old Order Amish with mean age (SD) 44.0 (17.0) years, with 1670 (57.8%) women. Heritability of T. gondii IgG titers and derived seropositivity was estimated using a mixed model with fixed effects for age and sex and random kinship effect. Potential environmental contributions were estimated using a likelihood ratio test with household included as an additional random effect.

**Results:** Of the participants, 1098 had positive antibody titers (54.4%). Heritability for T. gondii serointensity was estimated to be 0.22 (p=0.05E-08), and for T. gondii seropositivity 0.28 (p=1.9E-05). Household effects did not account for a significant proportion of phenotypic variance for either T. gondii serointensity or T. gondii seropositivity, regardless of whether heritability was included in the model. Nuclear household effects approached significance.

**Conclusions:** In the Amish, T. gondii seroprevalence (54.4%) was higher than previously reported in the US population (approximately 12%). Unexpectedly, heritability estimates of T. gondii serointensity or T. gondii seropositivity, regardless of whether heritability was included in the model. Nuclear household effects approached significance.

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**Keywords:** Toxoplasma gondii, Heritability, Mental illnesses, Old Order Amish

915. Epigenetic Mediation of Temporal Changes in Psychiatric Symptoms: A Pilot Study

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**Background:** Despite the toll psychiatric disorders have on modern-day society, we know relatively little on the mechanisms at the root of their emergence, progression and remission. Evidence indicates that DNA methylation plays a role in schizophrenia and mood disorders, although research relied mostly on cross-sectional designs. This pilot study describes changes in DNA methylation over time in relation to changes in psychotic and depressive symptoms in diseases related genes (e.g., BDNF, COMT1, FKBP5).

**Methods:** DNA from whole blood was extracted at hospital admission and discharge (22.04 days apart; SD=13.95) and DNA methylation profiles were characterized using Sequenom EpiTYPER. Participants’ diagnoses obtained from psychiatrists were used to select patients with bipolar or schizoaffective disorders (n=14) or schizophrenia and other psychotic disorders (n=14).

**Results:** Out of 232 CpGs that passed QC, linear mixed models correcting for age and gender detected 22 CpGs that varied over time (p ≤ 0.05), of which 13 had more than 2% of methylation difference between hospital admission and discharge. Moreover, 23 and 18 CpG sites were associated with improvement (or deterioration) of psychosis and depressive symptoms, respectively. Interestingly, the same findings were found when enlarging the temporal window to the beginning of the outpatient follow-up, on average, 65.94 (SD=37.88) days after hospitalization.

**Conclusions:** These preliminary findings suggest that epigenetic variations in blood might reflect to some extend the change in symptomatology over time. The Signature Databank may thus be advantageously positioned to better understand these epigenetic variations and their role in response to treatment.

**Supported By:** Foundation of the Research Center of the Montreal Mental Health University Institute

**Keywords:** DNA methylation, psychiatric disorders, longitudinal cohort, Emergency Center

916. Emergence, Remittance, and Persistence of Psychosis Symptoms in 22q11.2 Deletion Syndrome

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**Background:** Individuals with 22q11.2 deletion syndrome (22q11DS) are at markedly elevated risk for psychotic disorders. The dynamic nature of psychosis symptoms is investigated in youth with stable, emergent, remitted, and persistent psychosis symptoms. Demographic, clinical and cognitive predictors of psychosis are assessed.

**Methods:** Prospective follow-up over 2.8 years was undertaken in 75 individuals with 22q11DS aged 8-35 years. Mood, anxiety and attention-deficit hyperactivity disorders and psychosis symptoms were assessed with the Kiddie-Schedule for Affective Disorders and Psychosis and Scale of Prodromal Symptoms (SOPS). Factor analysis revealed positive and negative factors for psychosis symptoms. Cognition was evaluated with the Penn Computerized Neurocognitive Battery.

**Results:** Psychotic disorder or clinically significant SOPS positive rating were consistently absent in 35%, emergent in 13%, remitted in 22%, and persistent in 31% of participants. At baseline, the negative factor score is elevated in individuals who will experience emergent psychosis. Several negative symptoms also linger in individuals with remitted psychosis symptoms. Baseline global functioning is similar for those with emergent, remitted, and persistent psychosis. Emergence and persistence of psychosis is predicted by history of anxiety disorder while rise in total SOPS score and positive factor score were predicted by baseline history of mood disorder. Lower baseline global cognition and greater global cognitive decline were both predictive of psychosis outcomes.
Conclusions: Our results suggest that dysphoric mood and anxiety often accompany psychotic experiences and global cognitive deficits are predictive of psychosis in 22q11DS. Furthermore, negative symptoms and functioning should be taken into account when determining psychosis risk in this population.

Supported By: MH087626; MH087636; MH019112, K08 MH079364

Keywords: Schizophrenia Spectrum, Psychosis-Proneness, 22q11 Deletion Syndrome, longitudinal cohort, cognition

917. Genome-Wide Association Study (GWAS) of Toxoplasma Gondii Infection and Evaluation of Schizophrenia Polygenic Risk by Using a Polygenic Risk Score (PRS)

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Background: Toxoplasma gondii (TOXO) infects approximately 1.5 billion people worldwide. TOXO is implicated in a heightened risk for schizophrenia (SCZ). We performed a GWAS with TOXO in an Ashkenazi cohort of SCZ subjects. We then applied the schizophrenia polygenic risk score (SCZ-PRS) derived from the Psychiatric GWAS Consortium separately in TOXO-positive and TOXO-negative subjects to explore the hypothesis that SCZ subjects infected by TOXO will have less polygenic risk burden than uninfected subjects.

Methods: 790 individuals (519 SCZ-cases; 271 controls) were tested for TOXO positivity. Genotyping was performed using the Affymetrix-SNP-Array-6.0. The SCZ-PRS was calculated using PRSice separately in a) PRS-TOXO positive; b) PRS-toxo-negative samples (n negative and c) to establish type-2-error by randomly sampling PRSice separately in a) PRS-TOXO positive; b) PRS-toxo-negative subjects to explore the hypothesis that SCZ schizophrenia polygenic risk score (SCZ-PRS) derived from the top hits included a large number of genes involved in neurodevelopment and psychiatric disorders. The SCZ-PGS predicts SCZ as expected In the TOXO-negative group (n=662, p=10-4), but not in the TOXO-positive (n=128; p=0.354). In random samplings of the toxo-negative subpopulation to simulate equivalent power between groups, p>0.05 45% of the time, but p<0.354 only 2% of the time.

Conclusions: GWAS in this Ashkenazi cohort identified several genes potentially involved in vulnerability to TOXO. We found some evidence that the SCZ-PRS predicts SCZ status in TOXO-negative subjects but not TOXO-infected patients. Although the results are intriguing, we cannot currently rule out a type-2 error.

Supported By: NIH R01MH097475, R01MH0976764

Keywords: Polygenic Risk Score, Schizophrenia, Toxoplasma gondii, GWAS

918. Anterior-Posterior Gradient Differences in Lobar and Cingulate Cerebral Blood Flow in Late-Life Depression

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Background: Vascular pathology and dysregulation is common in late-life depression, contributing to altered cerebral blood flow (CBF) and potentially influencing cerebral pathology. Since aging is itself associated with changes in CBF, we sought to examine whether depressed elders exhibit differences in CBF from age- and sex-matched non-depressed subjects.

Methods: 22 elderly aged 60 years or older with Major Depressive Disorder and 19 with no psychiatric history completed cranial 3T MRI, including pseudo-continuous Arterial Spin Labeling (pCASL) acquisition. FreeSurfer parcellation of the brain identified frontal, temporal, parietal and cingulate sub-regions in which CBF was then calculated. White matter hyperintensities (WMH) were measured from FLAIR images.

Results: In models controlling for age, sex, and WMH volume, the depressed group exhibited lower normalized frontal lobe CBF (F=43.02, p<0.0001), but increased normalized CBF in the parietal (F=10.47, p=0.0027) and temporal lobes (F=20.96, p<0.0001). While no significant group difference was observed for CBF of the cingulate gyrus, CBF differed among cingulate sub-regions. Depressed subjects exhibited lower CBF in anterior regions, including the caudal (F=9.99, p=0.0032) and rostral (F=14.15, p=0.0006) anterior cingulate cortex, while they exhibited a higher CBF in the isthmus of the cingulate cortex (F=9.96, p=0.0033). CBF in the posterior cingulate cortex did not differ between groups.

Conclusions: Decreased frontal CBF in depressed elders might either be reflective of or contribute to decreased metabolic activity and parallels differences in anterior cingulate CBF. Parietotemporal increases in CBF may be a compensatory response to either frontal hypoperfusion or early neuro-cognitive pathology in those regions.

Supported By: NIH grants R21 MH099218 and K24 MH110598, and CTSA award UL1TR000445 from the National Center for Advancing Translational Sciences.

Keywords: Aging, Depression, MRI, ASL MRI

919. Anterior Cingulate Cortex Activity in Implicit and Explicit Emotion Regulation Predicts Cognitive Behavioral Therapy Response in Anxiety and Depression

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Background: The anterior cingulate cortex (ACC) predicts treatment response in anxiety and major depressive disorder (MDD). However, findings are largely based on emotion processing studies. Cognitive Behavioral Therapy (CBT) is empirically supported psychotherapy for anxiety disorders.
and MDD. In CBT techniques are aimed at improving emotion regulation. Therefore, baseline variance in ACC activity during regulation is hypothesized to predict CBT outcome as ACC is central to cognitive-emotion interactions.

**Methods:** A week before CBT, 22 with social phobia, 15 with MDD, and 13 with generalized anxiety disorder completed validated explicit and implicit emotion regulation tasks during fMRI. For explicit regulation, patients used cognitive reappraisal to downregulate emotional reactivity to aversive images. For implicit regulation, patients completed a threat interference paradigm comprising negative face ‘distractors.’ Pre-CBT activity was derived from an anatomy-based (MNI) bilateral ACC mask and responder status was defined as >50% reduction in primary symptom severity after 12 weeks of CBT.

**Results:** Primary symptom severity decreased following CBT (p<0.001) and across patients, 48% were ‘responders.’ For explicit regulation, less baseline ACC activity classified responder status (AUC=0.67, p=0.04) and activation negatively correlated with symptom reduction (r=-0.33, p=0.02). Regarding implicit regulation, greater baseline ACC activity classified responder status (AUC=0.67, p=0.038) and activation positively correlated with symptom reduction (r=0.40, p=0.01).

**Conclusions:** Findings suggest ACC predicts treatment response in a transdiagnostic sample. The direction of activation (reduced vs. enhanced) appears to depend on the neurocognitive probe of interest – explicit or implicit regulation. ACC as a predictor of CBT outcome has implications for precision medicine.

**Supported By:** K23; NARSAD; R01

**Keywords:** fMRI, Transdiagnostic, Prediction of Treatment Outcome, Psychotherapy, Anterior Cingulate Cortex

**920. Neural Correlates of Mentalizing and Uncertainty in Socially Anxious Adults**

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**Background:** Individuals with social anxiety tend to exhibit atypical cognitive biases. These biases include anticipation of social failure, especially under conditions of uncertainty, as well as beliefs that others will hold them to unreasonably high standards in social interactions. In the present study participants with social anxiety played the Prisoner’s Dilemma game in order to model brain activity associated with theory of mind and uncertainty.

**Methods:** 32 non-psychiatric volunteers (Ages 18-28) categorized using Liebowitz Social Anxiety Scale-Self Report (LSAS-SR) scores as having high or low trait anxiety, were scanned in a 3T Siemens scanner while playing the iterated Prisoner’s Dilemma task against a computerized confederate whom they were deceived to believe was a human co-player.

**Results:** There was a significant increase in activation within all feedback conditions in the temporoparietal junction (TPJ), the precuneus within all subjects (t(30)=2.5, p<.05). Highly anxious individuals exhibited an increased trend of activation in the TPJ but the relationship did not reach significance (t(30)=2, p<.05) during trials with diverging responses from the co-player. Highly anxious individuals also exhibited an increased trend in activation in the midcingulate cortex (MCC) (t(30)=2.5, p<.05) during anticipation periods.

**Conclusions:** While the analysis was nonsignificant, activation patterns in the TPJ hint at a tendency among anxious participants to devote more resources to reflection about other people’s thoughts. Anxious participants could also experience elevated feelings of discomfort when the outcome of an interaction is uncertain, as evidenced by the trend in MCC activity. Future research with larger samples would help address these possibilities more conclusively.

**Supported By:** CABI Seed Grant

**Keywords:** social anxiety, Prisoner’s Dilemma, Neuroimaging, Cognitive Neuroscience

**921. Influence of Age, Type, and Number of Trauma Exposures on the Neural Mechanisms of Conditioned Fear Extinction**

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**Background:** Psychopathology following trauma exposure is thought to arise from perturbations in the neural circuits underlying fear conditioning and extinction. The impact of trauma exposure on these mechanisms may depend on trauma-related characteristics. We present novel data on whether 1. age at trauma (childhood-adulthood), 2. number of traumas (single-multiple), and 3. trauma type (sexual-non-interpersonal) differentially affect the neurobiology of fear learning and extinction mechanisms.

**Methods:** Existing data of 71 trauma-exposed individuals were divided based on each research question. Participants underwent a fear conditioning, extinction, extinction recall, and renewal paradigm. Measurements included skin conductance responses (SCR) and fMRI. Region of interest analyses were restricted to the vmPFC, amygdala, hippocampus, insula and dorsal anterior cingulate cortex (pfwe<.05).

**Results:** During fear conditioning, both the childhood and sexual trauma groups showed blunted SCR and lower reactivity in threat-related regions, compared to adulthood and non-interpersonal trauma, respectively (F(1,41)=4.058, p=.05; F(1,37)=4.282, p=.046). The SCR-data further demonstrated reduced extinction retention in the childhood group (F(1,36)=3.986, p=.047). The sexual trauma group showed aberrant SCR during fear renewal, reflected by lower SCR to the danger stimulus (F(1,31)=6.081, p=.02). Both the childhood and sexual trauma group showed reduced vmPFC recruitment across extinction learning and retention phases. The single versus multiple trauma groups showed similar SCR and vmPFC activation across task phases.

**Conclusions:** The results show that sexual trauma and childhood trauma are linked to alterations in fear conditioning and extinction mechanisms. These characteristics may therefore be specifically linked to increased vulnerability for psychopathology, and to non-response to exposure-based therapies in individuals who developed psychopathology.
922. Reward Anticipation in Early Expression of Psychotic Disorder: A Functional MRI Approach

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Background: Previous research in patients with psychotic disorder has shown reduced activation in the brain’s reward system (ventral medial prefrontal cortex (VMPFC), ventral striatum (VS), nucleus accumbens, caudate, putamen, ventral tegmental area (VTA)). The literature on the reward system in subclinical psychosis is limited and inconclusive, describing both hypo- and hyper-activation. Therefore, reward anticipation in individuals with subclinical psychotic symptoms was further examined.

Methods: A sample of young adults aged 16-26 years (n=25) with subclinical psychosis and healthy controls (n=42) underwent fMRI scanning. The Monetary Incentive Delay task was conducted with cues related to win, loss or neutral conditions with three gain or loss levels (small: €0.10, medium: €0.60 and large €3.00). fMRI analysis was conducted using FSL’s General Linear Model on the reward versus neutral contrast. Whole brain analysis and region of interest (ROI) analysis on the VMPFC, VS and VTA was conducted. After extracting ROI data, statistical analysis was performed by regression analysis in STATA.

Results: Main effects of the large win (€3.00) > neutral contrast were found in both groups showing widespread brain activation. The PE > HC group comparison on the large win > neutral contrast showed significant increased activation in the left temporal pole. The ROI analysis revealed equal activation during reward anticipation between both groups.

Conclusions: The increased activation during reward anticipation in individuals with subclinical psychosis may point to mechanisms of plasticity and/or compensation. Reward related regions were not different during the anticipation phase, and suggests that the underlying dopamine dysregulation may be subtle in this phase.

Keywords: Psychotic Disorders, fMRI, reward anticipation, Monetary Gain, Prodrome

923. Maternal Caregiving Moderates Brain-Emotional Behavior Relationships in 3 Month Infants

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Background: The relationship between typical development of infant emotionality and brain measures, and moreover, how maternal caregiving might influence this relationship remains unclear. Finding biological correlates of temperament during infancy would not only better our understanding of brain-behaviour relationships, but may be helpful in predicting future psychological outcome empirically. Our aims were to (1) investigate the relationship between diffusion metrics and 3- and 9-month emotionality measures, and (2) examine whether this relationship is moderated by maternal caregiving.

Methods: Mother-infant dyads were recruited through the Pittsburgh Girls Study. Diffusion tensor images were collected at 3 months and mother-infant interactions were collected at 3 and 9 months. Deterministic tractography was performed using ExploreDTI. General linear models were developed to examine the relationship between diffusion measures, including fractional anisotropy (FA), longitudinal and radial diffusivity, and infant temperament. Next, maternal caregiving measures were tested for moderating effects.

Results: Here we found a (1) positive relationship between FA of the right uncinate fasciculus and 3 month negative to positive emotionality ratio [F(1,22)=5.57, p=0.028], (2) positive association between FA of the left uncinate fasciculus and 9 month self soothability [F(1,12)=16.5, p=0.0016], and (3) moderation effect of maternal sensitivity on relationship (1) [F(3,20)=3.83, p=0.016].

Conclusions: Our results provide evidence for a relationship between diffusivity in the uncinate fasciculus and infant temperament measures at 3 and 9 months. Moreover, this relationship appears to be enhanced with greater maternal sensitivity. Our results suggest the importance of emotional experience and maternal care for the development and refining of emotional circuits.

Supported By: NIH R21

Keywords: Diffusion Tensor Imaging (DTI), Infant Temperament, Maternal sensitivity, Predictive Analytics, structural neuroimaging

924. Socioeconomic Status in Early Childhood Predicts White Matter Integrity in Young Adulthood

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Background: Socioeconomic disadvantage confers higher risk for medical illness, psychiatric distress, and poor cognitive functioning (Gianaros, 2013). Changes in brain structure may be one mechanism linking low socioeconomic status (SES) to poor health outcomes (Ursache & Noble, 2016). Concurrent associations between SES and white matter microstructure have been reported in childhood (Ursache & Noble, 2016), late adolescence (Noble et al., 2013), and adulthood (Gianaros et al., 2013) in the cingulum, a pathway implicated in executive functioning and self-regulation. Longitudinal investigations are necessary to determine whether SES in early life can impact white matter microstructure later in development.

Methods: High-risk male participants (N=158) were recruited in infancy based on low family income and followed until young adulthood as part of the Pitt Mother & Child Project.
925. Global Probabilistic Tractography and Symptom Dimensions in a Prospectively Characterized Sample of Adults with a Childhood Diagnosis of Attention Deficit-Hyperactivity Disorder

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Background: White matter abnormalities have been shown to play an important role in the pathophysiology of Attention Deficit-Hyperactivity Disorder (ADHD). However, little is known about the extent to which ADHD symptom severity is associated with abnormalities in white matter tracts known to be involved in attention and emotional control processes.

Methods: We aimed to determine if abnormalities in fronto-temporal white matter tracts involved in attention (superior longitudinal fasciculus, SLF) and emotional control processes (uncinate fasciculus, UF) relate to clinically relevant symptom-dimensions in 46 adults with or without ADHD (32 ADHD, 14 non-ADHD; mean age[SD]=33[3] years, 44males), recruited from an ongoing longitudinal study in 347 children with ADHD prospectively characterized from-youth-to-adulthood. Symptom-dimensions of inattention, hyperactivity/impulsivity (H/I), and anger-irritability (A/I) were used. Global probabilistic tractography was used to reconstruct SLF and UF. Volume, length, and diffusivity metrics were extracted for each participant.

Results: ADHD, vs non-ADHD, adults showed smaller volume in the right UF (p = .05) and right SLF (p = .06). In ADHD adults, H/I symptoms were negatively correlated with length in the SLF (left: r = -.40, p = .01; right: r = -.40, p = .03) and A/I symptoms were positively correlated with volume of the right UF (r = .40, p = .04).

Conclusions: Findings suggest that higher volumes in fibers connecting medial-temporal and orbitofrontal regions might be associated with higher severity of A/I symptoms. Abnormal reorganization of the fibers connecting DLPFC and temporo-parietal regions, as evidenced by a shorter length in the SLF, may represent a neurobiological substrate of higher levels of H/I symptoms, possibly associated with inability of modulating thoughts and actions in goal-directed behaviors reported in ADHD.

Supported By: NIH R01 DA026222
Keywords: socioeconomic status, diffusion MRI, longitudinal, Neurodevelopment

926. Regional Differences and Demographic Correlates of Cerebrovascular Reactivity Among Healthy Adolescents

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Background: Cerebrovascular reactivity (CVR), a proxy of cerebrovascular health, is reduced in adult depression. Breath-holding (BH) paradigms alter vasoactive CO2, are well tolerated, and produce robust CVR measures in adults. We therefore look to extend BH-CVR to a healthy adolescents (HA) sample, investigating two modelling approaches, evaluate regional differences in BH-CVR, and examine BH-CVR in relation to demographics (e.g. sex).

Methods: Thirty-nine HA (ages 13-20 years, 20 females) completed six 15-second BHs, alternating with 30-second free-breathing intervals. Blood-oxygenation-level dependent (BOLD) fMRI at 3-Tesla measured CVR voxel-wise and in five major brain subdivisions. Hemodynamic responses were modelled using a: 1) double-gamma variate convolved with a boxcar function with an individualized delay term (HDR-Delay), and 2) a sine-cosine regressor with a delay term. CVR-delay was the elapsed time between end of BH and peak BOLD signal.

Results: There were regional differences in CVR (Frontal >Occipital >Parietal >Temporal >Subcortical) and CVR-delay (Occipital >Parietal >Frontal >Temporal >Subcortical). Males had higher CVR than females (p = .03, partial η² = .35). Comparing both models, the HDR-Delay method yielded a significantly superior model fit and marginally larger cluster volume than the sine-cosine regressor.

Conclusions: This study found regional CVR differences in HA, which can inform future studies of adolescents with brain- and/or vascular-related diseases. Our regional CVR hierarchy findings were consistent with prior healthy adult studies, except for the relatively higher frontal CVR. Lower CVR in females converges with prior evidence of higher basal cerebral blood flow. Both methods for modelling the raw CVR data were effective, albeit the HDR-Delay method was marginally superior.

Supported By: Ontario Mental Health Foundation

Keywords: Cerebrovascular Reactivity, Breath-Hold, Magnetic resonance imaging, Healthy subjects, Adolescents
927. Subcortical Volume and Neural Connectivity in Youth with Psychosis Spectrum Symptoms

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Background: Altered subcortical region volumes, specifically in the thalamus and striatum, as well as cortico-thalamic-striatal-cortical (CTSC) connectivity have been observed in schizophrenia.

Methods: In this study, structural magnetic resonance imaging was used in a child and youth sample (n=821) including children with psychosis spectrum (PS) symptoms (n=110) to further understanding of these biomarkers and their presentation in youth outside of high risk groups. Subfields of subcortical regions were identified using the segmentation tool MAGeTbrain. Correlations between these subfields and cortex-wide cortical thickness values were used to infer network connectivity.

Results: Boys and girls were examined separately. Volumes of the globus pallidus and striatal subregions were found to be increasing in boys with PS, but not in typically developing male youth (right globus pallidus: r(TD)=-0.21, t(age by psychosis)=−2.38, p=0.017). A similar increase in volumes in girls with PS was seen in thalamic subregions but not in those who were typically developing (left lateral dorsal area: r(PS)=0.28, t(age by psychosis)=−2.95, p=0.009). Preliminary analyses also indicate that putamen subregions in psychosis spectrum boys are negatively correlated with cortical thickness in the bank of superior temporal sulcus, precenetal gyrus in the posterior frontal lobe and superior parietal lobe. Thalamic subregions in psychosis spectrum girls were negatively associated with cortical thickness in the insula.

Conclusions: These findings indicate early alteration of neural circuitry in PS youth similar to what is observed in schizophrenia and provides the opportunity to improve on early interventions by targeting gender and critical developmental time points.

Keywords: Structural MRI, Early psychosis, Connectivity, Subcortical, Sex-specific

928. Cortical Abnormalities Associated with Pediatric and Adult Obsessive-Compulsive Disorder: Findings from the Enigma Obsessive-Compulsive Disorder Working Group

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Background: Brain imaging studies on structural abnormalities in OCD have been inconsistent, partially due to limited statistical power, clinical heterogeneity, and methodological differences. Here, we present data of the largest study to date on cortical brain measures in OCD patients and healthy controls by using meta- and mega-analyses.

Methods: Structural T1-weighted MRI scans including 1905 OCD patients and 1760 healthy controls from 27 sites worldwide were processed locally using FreeSurfer 5.3. Effect
929. Shared and Disorder-Specific Neural Dysfunction during Sustained Attention in Adolescent Attention-Deficit/Hyperactivity Disorder and Obsessive/compulsive Disorder

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Background: Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) and obsessive/compulsive disorder (OCD) share deficits in attention. The aim was examine whether brain activation abnormalities underlying sustained attention in the two disorders were shared or disorder-specific.

Methods: Twenty boys with ADHD, 20 boys with OCD and 20 healthy controls aged between 12-18 years completed a functional magnetic resonance imaging (fMRI) version of a sustained attention task with a progressively increasing attention load. Performance and brain activation were compared between groups.

Results: A group by delay interaction analysis showed that OCD patients had disorder-specific underactivation in middle anterior cingulate, while ADHD patients showed disorder-specific underactivation in left dorsolateral prefrontal cortex/dorsal inferior frontal gyrus relative to controls and each other. ADHD and OCD patients shared left insula/ventral IFG underactivation and increased activation in posterior default mode network (DMN) regions, but had disorder-specific overactivation within anterior DMN regions, in dorsal anterior cingulate for ADHD and in anterior ventromedial prefrontal cortex for OCD. Only ADHD patients were impaired in performance.

Conclusions: Findings suggest that sustained attention in both disorders relative to controls is associated with decreased recruitment of regions of task-positive salience and attention networks, as well as increased activation in DMN regions. However, the specific regions showing abnormalities in each disorder were disorder-specific, with disorder-specific underactivation in ADHD in task-relevant lateral prefrontal cortex and in OCD in medial frontal cortex, and hyperactivation in both disorders in different frontal parts of the DMN.

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Keywords: ADHD, OCD, fMRI, Sustained attention, Disorder-specificity

930. Altered Neural Anticipation of an Aversive Interceptive Experience in Women Remitted from Bulimia Nervosa

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Background: Altered function of the neural circuits supporting body state processing, or interoception, may contribute to bulimia nervosa (BN). However, data suggest both hyper- and hyporesponsivity to interoceptive stimulation in BN. Studies using pleasant stimuli indicate that aberrant signaling during the anticipation or processing of interoceptive events may explain these mixed findings. We examined whether BN is associated with altered activation before, during, and after an unpleasant interoceptive experience.

Methods: Women remitted from BN (RBN; n=25) underwent fMRI during an inspiratory breathing load paradigm. T-tests compared group activation in interoceptive search regions of interest (voxel-wise p < 0.01, cluster-wise p < 0.05, corrected). Exploratory Huber robust regressions examined BOLD associations with clinical measures.

Results: During breathing load anticipation, RBN relative to CW showed increased activation in bilateral mid-insula, left superior
frontal gyrus (SFG), bilateral putamen, right mid-cingulate, and left posterior cingulate cortex (PCC). Group responses did not differ during or after the breathing load. Increased anticipatory putamen activation was associated with greater reward dependence, and anticipatory activation in SFG, putamen, and PCC was inversely associated with months of bulimic symptom remission.

**Conclusions:** Hyperactivation during the expectation of an aversive interoceptive experience could represent an exaggerated prediction error signal. This signal may sensitize individuals to changes in interoceptive state and could contribute to or result from repeated binge-eating/purge episodes. Conceptualizing BN as a disorder of aversive interoceptive instability may inform new interventions targeted at regulating interoceptive experiences.

**Supported By:** R01 MH042984; The Price Foundation

**Keywords:** Interoception, Bulimia Nervosa, fMRI

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**931. More Efficient Brain Connectivity Network in Veterans with Suicide Attempt**

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**Background:** Suicide is a public health concern for United State veterans and civilians. Prior research has shown neurobiological factors in suicide; however, studies of neuroimaging correlates of suicide risk have been limited. The current study applied complex weighted network analyses to characterize the neural connectivity in white matter in veterans with suicide behavior.

**Methods:** Eighty veterans (64 males, 16 females) with a mean age of 36.9 years completed diffusion tensor imaging and a clinical battery including the Columbia Suicide Severity Rating Scale (C-SSRS). Participants included 28 veterans without suicidal behavior, 29 with only suicidal ideation, and 23 with suicide attempt. Structural connectivity networks among 82 parcellated regions were produced using whole-brain tractography. Global and nodal metrics of network topology including efficiency and nodal degree were calculated among three groups.

**Results:** Veterans with a history of suicide attempt had shorter characteristic path length and greater global efficiency and mean weighted degree of global network metrics (p < 0.024). Suicide attempters had sixteen hubs among 82 cerebral nodes, whereas the no suicide and suicide ideation groups had 12 hubs. Moreover, the left posterior cingulate cortex showed significantly greater weighted degree in veterans with suicide attempt relative to others (p<0.0003).

**Conclusions:** Veterans with suicide attempt had more efficient connectivity networks and more hub regions in the brain; these findings may be distinctive neurobiological markers for individuals with suicide attempt. Strong connectivity in the left posterior cingulate cortex may be implicated in traumatic autobiographic memory recall in veterans with suicide attempt.

**Supported By:** Military Suicide Research Consortium (MSRC)

**Keywords:** Suicide, Diffusion Tensor Imaging (DTI), Veterans, Brain networks, Brain connectivity

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**932. Proton Brain GABA and Suicidal Behavior in Veterans**

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**Background:** Studies investigating the neurobiological correlates of suicidal behavior have not provided conclusive results; thus, examinations of changes in neurochemistry that correspond with suicidal behaviors (SB) are limited. Although men have a higher rate of suicide completion, partly due to more violent methods, and women have a higher rate of suicide attempts, sex differences in the neurobiological underpinnings of suicide are not well understood. The current study evaluated the relationship between brain chemistry in the anterior cingulate cortex (ACC), a brain region implicated in suicide, and suicide behavior in female compared to male veterans.

**Methods:** Eighty-one veterans (16 females, mean age=37.15 years) were scanned on a 3T Siemens VerioTM whole-body MRI scanner. MRS data were acquired from the voxels positioned bilaterally within the ACC. MRS neurochemical profiling included analysis of creatine (Cre), N-acetyl aspartate, and GABA. Participants also completed a clinical battery including the Columbia Suicide Severity Rating Scale (C-SSRS).

**Results:** Female veterans with SB showed lower GABA/Cre (p=0.04) compared to female veterans with no SB. Furthermore, HAM-A scores negatively correlated with GABA/Cre (p=0.02) in female veterans but not in male veterans.

**Conclusions:** These preliminary data suggest altered neurochemistry in female veterans with a history of suicidal behavior and highlight sex-specific metabolite changes. In agreement, previous studies showed reduced expression of GABA-A receptors in suicide descendents; collectively suggesting that dysfunction in GABAergic transmission may contribute to SB, especially in females. Replication of these results would suggest specific treatment approaches targeted at females compared to males.

**Supported By:** Military Suicide Risk Consortium & Salt Lake City MIRECC

**Keywords:** Suicide, Proton Magnetic Resonance Spectroscopy, GABA

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**933. Entropy Analysis Shows Temporal Pole Diffusivity Changes in Bipolar Disorder**

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Recent Background: Whereas many MRI studies of bipolar disorder (BD) pathophysiology have focused on disruptions in white matter connectivity in the limbic system and prefrontal cortex, few have examined the role of the temporal pole. This represents a gap in the literature, as damage to the temporal pole has been seen to lead to BD in previously healthy patients. We analyzed white matter connectivity in the temporal pole of BD patients in the depressive phase of the illness compared to matched controls.

Methods: 18 subjects were included in this study; 9 were bipolar patients experiencing a current major depressive episode and the remaining 9 were age- and sex-matched controls. All images were acquired using a Siemens 3T Trio with a 12 channel head matrix coil. Average mean diffusivity (MD) of left temporal pole voxels and distribution entropy of MD were examined for group-wise differences between BD and healthy controls. All images were acquired using a Siemens 3T Trio.

Results: There was no statistically significant difference in average MD values between BD and healthy controls \( (p=0.40) \). The distribution of MD values was seen to be noticeably narrower in the BD group. Thus the entropy of the MD distributions was compared, and seen to be significantly reduced in BD \( (p=0.011) \).

Conclusions: Temporal pole diffusivity is more homogenous in the temporal pole of BD patients, possibly suggesting a loss of fine white matter organization in the region. It is not clear if this would be a precursor or result of symptomology, more study is warranted.

Supported By: NIH R01MH090276

Keywords: bipolar disorder, MRI brain imaging, diffusion imaging

934. Cortical and Subcortical Morphometry Predicts Relapse of Depressive Symptoms following Electroconvulsive Therapy

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Background: Recent findings indicate that acute clinical outcome following treatment for major depressive disorder (MDD) with electroconvulsive therapy (ECT) is predictable from pre-treatment neuroimaging measures. However, prediction of long-term relapse risk has not previously been addressed. Here we used random forests (RF) to predict individual depression relapse within 6-months following ECT in two independent cohorts.

Methods: MDD patients eligible for ECT were recruited from the University of California, Los Angeles (UCLA) and the University of New Mexico (UNM). Patients received structural scans and mood evaluations 24 hours prior to ECT (T1), within a week of completing ECT (T2), and 6 months post T2 or at relapse (T3). The Hamilton Depression Rating Scale (HAM-D) tracked symptom severity. Relapse was defined by (i) \( \geq 50\% \) reduction of HAM-D over index and (ii) T3 HAM-D \( \geq 17 \). At UCLA and UNM, 6/17 and 13/25 patients relapsed, respectively. RFs with repeated leave-one-out cross-validation modeled relapse risk using either pre- or post-treatment cortical thickness and subcortical volumes or change in these measures over index.

Results: The mean balanced accuracy (mean of sensitivity and specificity; BA) of models based on T2 measures was 77% and 73% for UNM and UCLA, respectively. T1 measures yielded a mean BA of 56% at UCLA and 71% at UNM. Structural changes between T1 and T2 provided a mean BA of 74% at UCLA and 61% at UNM.

Conclusions: Our findings suggest symptom relapse prediction post-ECT is feasible. Currently post-treatment measures are most informative, however, pre-treatment prediction is more desirable to accelerate clinical decisions.

Supported By: R01MH111826-01; P20GM103472-01; R01MH092301

Keywords: Major Depressive Disorder (MDD), Electroconvulsive therapy (ECT), Relapse Risk, Classification algorithms, Biomarkers

935. Acute Cortisol Reactivity is Associated with Increased Connectivity from Default Mode to Cognitive Control Networks in Remitted Adolescent-Onset Depression

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Background: Glucocorticoids are one proposed mediator of medial prefrontal cortex regulation of limbic response to stress. In depression, cortisol reactivity attenuates frontal-subcortical activation in response to the mild acute stressor of emotional/cognitive challenges during fMRI. Sensitivity of neural networks to stress may persist after remission of clinical symptoms but has not yet been studied.

Methods: We assessed pre-scan cortisol levels and resting state functional connectivity (RSFC) of limbic seed regions dense in glucocorticoid receptors (bilateral subgenual anterior cingulate [sgACC], posterior cingulate [PCC], and anterior hippocampus [antHPF]) among 33 healthy controls (HC, 18-29 years old) and 29 age-matched participants in remission from major depression or bipolar disorder. Whole-brain corrected regression models investigated modulation of connectivity by cortisol concentration and diagnosis.

Results: In remitted depressed participants, but not HCs, cortisol was positively associated with hyper-connectivity from bilateral sgACC and PCC seeds to lateral parietal and frontal regions of the cognitive control network (CCN), the right middle temporal gyrus, and left anterior insula. Similarly, in remitted participants, cortisol predicted hyper-connectivity of the bilateral antHPF to frontal and parietal regions of the CCN; cortisol predicted within network hyper-connectivity to the ipsilateral parahippocampal and inferior temporal gyri from the left antHPF seed.

Conclusions: The effect of cortisol on communication between salience and executive brain networks differs between asymptomatic individuals with and without a history of depression.
Exaggerated acute cortisol response may reflect frontal regulation of neural sensitivity to stress in remitted participants, possibly indicative of compensatory mechanisms of resilience, persistent trait markers of depression risk, or accumulated scar dysregulation.

**Supported By:** NIMH R01 MH091811 (Langenecker); NIMH R01 MH101487 (Langenecker); F31 MH108258 (Peters)

**Keywords:** cortisol reactivity, Resting state fMRI, Depression

936. Cortical Thickness as a Biomarker of Repetitive TMS Treatment Response in Depression

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**Background:** Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for medication-refractory major depressive disorder, yet the mechanisms of action for this intervention are poorly understood. Here we evaluated cerebral cortex thickness in response to rTMS treatment as a possible biomarker of treatment response.

**Methods:** We evaluated cerebral cortex thickness longitudinally over a 4-6 week depression treatment course of left dorsolateral prefrontal cortex (DLPFC) 10 Hz rTMS. MRI and Hamilton Depression Rating Scale (HamD) were acquired before and after treatment. The longitudinal processing stream of FreeSurfer was used to optimize detection of changes in cerebral cortex thickness in the same individual across two time points, before and after rTMS.

**Results:** 38 patients with medication-resistant major depression participated, 30 female, age 46 +/- 14. Symptoms improved from pre- to post-rTMS (24 +/- 7 to 15 +/- 8; P < 0.001). There were no global changes in overall cortical volume or average cortical thickness. A comparison of cortical thickness difference from pre- to post-rTMS between responders (N=14) and non-responders showed a significant increase in thickness of the left prefrontal cortex in responders relative to non-responders, P < 0.001, uncorrected for multiple comparisons.

**Conclusions:** Increased left DLPFC thickness is associated with effective rTMS treatment for major depression and may serve as a biomarker of treatment, distinguishing responders from non-responders. Future work aims to increase the sample size as well as evaluate hippocampus volume changes.

**Supported By:** K12 Child Health Research Career Development Award; K23NS083741; UL1 RR025758

**Keywords:** rTMS, Major Depression, Structural MRI, Biomarkers, Neuromodulation

937. EEG Correlates of Real-Time fMRI Neurofeedback Amygdala Training in Depression

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**Background:** Real-time fMRI neurofeedback (rtfMRI-nf) training to upregulate amygdala hemodynamic activity during positive autobiographical memory recall decreases depressive symptoms. The current analysis characterized the EEG signal correlated to the fMRI amygdala signal during rtfMRI-nf training in order to translate amygdala rtfMRI-nf into a more portable and cheaper EEG-only intervention.

**Methods:** 26 depressed patients recalled positive memories while upregulating hemodynamic activity in an amygdala (n=13) or parietal (n=13) region during rtfMRI-nf training. 32-channel EEG recordings were collected simultaneously with fMRI. After removing MRI and cardioballistic artifacts, a continuous wavelet transform was applied to obtain EEG signal power for each channel in four frequency bands. Linear regression predicting the amygdala signal during happy memory/upregulate blocks was performed for each participant, reserving the last 20% of each participant’s data for model testing. Beta weights for each channel and frequency band were combined into a single data set to perform a one-sample t-test comparing each value to 0.

**Results:** Overall training-set = 0.74 (SD = 0.08), rtest-set = 0.23 (SD = 0.11). Beta weights for the following electrodes were significantly different from 0 after Bonferroni-correction for multiple comparisons (pcorrected < 0.001): Theta band: Fp2, F4, F7, F8, Pz, FC6. Alpha band: C4, C3, P3, CP5. Beta band: C3, CP2. Gamma band: FP2, F3, C4, P4, O2, F8, T7, CP2, FC5, CP5, CP6.

**Conclusions:** Using concurrent EEG measured during amygdala rtfMRI-nf training to increase activity during positive memory recall, we were able to identify EEG correlates of amygdala hemodynamic activity. This included many electrodes in the gamma band, associated with cognitive function. Results suggest translating amygdala rtfMRI-nf into an EEG intervention may be feasible

**Supported By:** NIMH K99MH101235; NARSAD Young Investigator Grant

**Keywords:** Amygdala, real-time fMRI neurofeedback, Concurrent EEG/fMRI, positive memory recall, Major Depression

938. Cortical Volume, Thickness and Surface Area in Adolescents across the Bipolar Spectrum


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**Background:** Diagnosis of Bipolar Disorder (BD) remains clinical, and its division into subtypes is based on severity and duration of manic symptoms. Little is known about neurostructural correlates of BD subtypes, especially in youth. Shared loss of gray matter volume in prefrontal regions was identified in adults with BD-I and –II, with more
severe deficits in BD-I. We aimed to compare cortical volume, thickness and surface area in adolescents with BD in regions previously found to be implicated in BD circuitry.

**Methods:** T1-weighted images of 44 adolescents with BD spectrum (14 BD-I, 16 BD-II and 14 BD-NOS) were obtained using 3T-MRI. Using FreeSurfer software, regions of interest (ROI) including ventrolateral prefrontal cortex (vPFC), ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (aACC), subgenual cingulate (sgCC) and amygdala were examined. Analyses were controlled for age, sex and total intracranial volume. A whole brain vertex wise exploratory analysis was also performed.

**Results:** aACC showed group differences (F= 4.115, p = .024, η²=.174) with BD-II showing lower cortical thickness than BD-I (p = .034) and BD-NOS (p = .010). No other group differences were identified. Whole brain analysis found lower cortical thickness in left medial OFC for BD-I/II group compared with BD-NOS.

**Conclusions:** This study found limited neurostructural differences amongst bipolar subtypes in adolescents, with lower cortical thickness in aACC in BD-II, and in OFC for combined BD-I/II compared to BD-NOS. This suggests additional deficits in the classical BD subtypes than in BD-NOS. Further neurostructural differences between subtypes may emerge later during the course of illness. Further MRI studies of phenotypical differences are warranted.

**Supported By:** Ontario Mental Health Foundation

**Keywords:** Bipolar Spectrum Disorders, Structural MRI, Adolescents, Pediatric Bipolar Disorder, Neuroimaging

**939. Identifying Clinically Relevant Electroencephalography Coherence Patterns in Major Depressive Disorder: Results from the EMBARC Study**

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**Background:** Recent research has aimed to identify predictors/biomarkers of treatment response and remission in Major Depressive Disorder (MDD) using electroencephalogram, which has shown some success. With a move to investigate network level brain function, additional studies have been conducted using EEG coherence to investigate coupling between regions, which makes for promising markers to investigate in MDD.

**Methods:** Participants consist of 40 healthy controls (HC) and 200 MDD patients before starting medication as part of the EMBARC study. Participants were scanned at one of four sites, and the resting-state EEG was acquired. Multiple factor analysis (MFA) was used to analyze coherence data. MFA analyzes (1) relationships between the data, (2) similarities between participants, (3) how each data table contributes to the analysis, and (4) stability and reliability of results using bootstrap (p < .05). MFA used coherence data across 4 frequency bands (alpha, beta, delta, and theta) as a function of group, MDD severity and MDD symptoms (e.g., anxiety).

**Results:** HC had tighter coupling of frequency bands (greater connectivity) than participants with MDD. Within MDD, as the level of depression severity increased, coupling of frequency bands became weaker (lower connectivity). The same was not true for all symptoms investigated. Interestingly, higher levels of anxiety showed tighter coupling (greater connectivity).

**Conclusions:** The present work provides evidence of clinically relevant coherence patterns in EEG within MDD. Coupling between regions and their clinical modifiers could be used as promising markers for treatment response, and will be further investigated in the final EMBARC sample.

**Supported By:** NIMH

**Keywords:** Major Depressive Disorder (MDD), Electroencephalography, Coherence

**940. Neuroimaging Biomarkers of Treatment Response in Major Depressive Disorder: An Activation Likelihood Estimation (ALE) Meta-Analysis**

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**Background:** Functional neuroimaging is increasingly used in the search for biomarkers of treatment response in major depressive disorder (MDD). To evaluate the translational potential of these biomarkers, a quantitative assessment of their consistency is needed. In this work, we conducted a meta-analysis of neuroimaging biomarkers using an activation likelihood estimation (ALE) approach.

**Methods:** We identified 684 records for screening using a literature search on PubMed and reference lists of prior reviews. Of these records, 17 articles met inclusion criteria. Our primary analysis was composed of 102 significant activation foci, reported by coordinate locations in the brain, using a total of 407 unique subjects. Additionally, subanalyses were performed separately for positive and negative predictors as well as task-related predictors.

**Results:** A pooled analysis of all treatment predictors identified the right anterior insula as a region in which pre-treatment activation was significantly associated with treatment response; this region was also found to be significant when focusing on negative treatment predictors. The posterior cingulate cortex (PCC) was identified in sub-analysis focusing on positive treatment predictors. Finally, a sub-analysis focused on tasks with emotional stimuli identified the subgenual cingulate in addition to the anterior insula and PCC.

**Conclusions:** Our results provide evidence for the consistency of activation in three regions as biomarkers of treatment response. This includes the right anterior insula as a negative predictor and the PCC as a positive predictor. Additionally, the relation between activation in these regions and post-treatment
outcomes appears to be driven largely by task-related activations, particularly those using emotional stimuli.

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Keywords: Major Depressive Disorder (MDD), brain imaging (FDG-PET/fMRI), Prediction of Treatment Outcome, Meta-analysis

941. White Matter Microstructural Differences in Major Depression: Meta-Analytic Findings from Enigma-MDD DTI

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Background: Disruptions in white matter (WM) integrity in major depressive disorder (MDD) have been widely reported (1, 2). As image processing techniques and sample sizes vary, results are difficult to compare across studies. The ENIGMA-MDD DTI Working Group aims to identify robust WM abnormalities for MDD patients worldwide, using harmonised techniques.

Methods: We analyzed DTI data from 565 controls and 649 patients from 13 sites with a mean age of 29 years (SD=13.8) and 62% female. The ENIGMA-DTI protocols were run on fractional anisotropy (FA) maps, as detailed online: http://enigma.ini.usc.edu/protocols/dti-protocols/. The average FA within each of 24 bilateral WM regions of interest (ROIs) was extracted. For each site, Cohen’s d measures for all ROIs were computed, with age, sex and their interactions included as covariates. A random effects meta-analysis was conducted to combine results across sites.

Results: The largest effect sizes were observed for the inferior fronto-occipital fasciculus (IFO; d=-0.2, p=0.02) and the corpus callosum (CC; d=−0.2, p=0.02), followed by the body of the corpus callosum (BCC; d=−0.19, p=0.028), followed by the body of the corpus callosum (BCC; d=−0.19, p=0.02), however, these results were non-significant after Bonferroni correction for multiple testing.

Conclusions: In the largest meta-analysis of DTI measures in MDD using harmonized protocols, we observed trends towards reduced FA in the inferior fronto-occipital fasciculus and the corpus callosum. Future meta-analyses in a larger sample will also assess moderating effects of other demographic and clinical covariates, including age of onset, stage of illness, number of episodes and symptom severity.

Supported By: NIH Big Data to Knowledge (BD2K) award (U54EB020403)

Keywords: Diffusion Tensor Imaging (DTI), Meta-analysis, Major Depressive Disorder (MDD), structural neuroimaging, Depression

942. Significant Overlap between Brain Maps Determined via Spatial Permutation

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Background: With the increasing use of big data in psychiatric neuroimaging, a common finding is spatial coherence or overlap between brain maps from different experimental contexts. Such findings may be problematic, however, because anatomically proximal brain areas tend to have elevated anatomical and functional similarity, inflating apparent overlap. We address this issue with a spatial permutation framework, using meta-analytic patterns of functional activation in depression as a test case.

Methods: Neurosynth (http://neurosynth.org) generated 15 automated meta-analyses of imaging coordinates associated with ‘depression’ or other terms including ADHD, alcohol, anxiety, empathy, impulsivity, language, memory, pain, PTSD, schizophrenia, self and stress. Cortical representations of these ‘reverse inference’ maps were projected onto FreeSurfer spherical coordinates. These spheres were permuted with angular rotations to generate null distributions of overlap.

Results: Depression had heterogeneous overlap with other maps (Pearson’s correlation, range -0.19 to 0.48). Parametric ‘significance’ of these correlations appears high even for correlations close to 0, driven by the large number of vertices (falsely) assumed to be independent. However, using spatial permutation the null hypothesis is rejected only in 5 of 14 cases: anxiety, PTSD, reward, schizophrenia and stress (1000 permutations, family wise error P < 0.05). Overlap between mental illnesses appears to stem from shared signal in medial prefrontal cortex.

Conclusions: It is critical to rigorously evaluate claims of convergence between brain maps. Spatial permutation tests provide the ability to account for spatial auto-correlation and to rigorously evaluate claims of convergence between disparate statistical maps.

Supported By: R25

Keywords: fMRI, Meta-analysis, Systems Neuroscience, Brain networks, Biostatistics

943. White Matter Integrity in Medication-Free Women with Peripartum Depression: Diffusion Tensor Imaging Study Using Tract-Based Spatial Statistics

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Keywords: Diffusion Tensor Imaging (DTI), Meta-analysis, Major Depressive Disorder (MDD), structural neuroimaging, Depression
Background: Peripartum Depression (PPD) affects 1 in 8 women and has debilitating effects on mother and child. Initial imaging studies in major depressive disorder (MDD) and PPD suggest overlapping structural and functional abnormalities. Diffusion tensor imaging (DTI) studies in MDD show decreased structural connectivity in the genu of the corpus callosum (CC) and left anterior limb of the internal capsule (L-ALIC), but no DTI studies exist in PPD. We analyzed fractional anisotropy (FA) as a measure of white matter integrity (WMI) of these two tracts using tract-based spatial statistics.

Methods: 31 pregnant, medication-free women, ages 18-40, were evaluated with the Hamilton Depression Rating Scale (HAMD) and a Structured Clinical Interview for DSM-IV at time of enrollment and time of magnetic resonance imaging (MRI). Structural MRI MP-RAGE and DTI sequences were acquired 1-10 weeks postpartum. Tract-based spatial statistics data was analyzed between healthy postpartum women (n=18) and women who developed PPD (n=13) to determine differences in WMI within the genu of the CC and L-ALIC. Results were corrected for multiple comparisons and analyses conducted using FSL, p<.05, K>10.

Results: Lower FA in both tracts (both p<0.05) was associated with a diagnosis of PPD compared to healthy women. Across both groups, FA was negatively correlated with HAM-D scores in the L-ALIC (p<0.05).

Conclusions: Reduced WMI in the genu of CC and L-ALIC could represent a structural predisposition to developing depression in the peripartum period. Our preliminary results in PPD are consistent with recent DTI studies of MDD outside of the peripartum period.

Supported By: K23MH097794 (KMD)

Keywords: Diffusion Tensor Imaging (DTI), Postpartum Depression, Major Depressive Disorder (MDD), Tract-Based-Spatial-Statistics (TBSS), Women

944. Structural Connectivity Correlates of CBT and SSRI Response in a Transdiagnostic Sample: A Preliminary RDoC Study

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Background: There have been several studies that have identified white matter (WM) abnormalities across a range of psychiatric disorders, however few studies have examined whether these WM alterations change with treatment. The purpose of the present study was to examine the structural connectivity correlates of treatment response to cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) in a transdiagnostic sample.

Methods: A sample of participants from a larger ongoing study was selected for WM connectometry analysis, comprised of 11 healthy controls (age 25.8±11.3, M=8F) and 21 patients (age 29.5±10.6, M=15F). Patients received 12 weeks of either CBT (n=10) or SSRI treatment (n=11) and were assessed/scanned at the beginning and end of the 12-week period. DTI diffusion scans with a total of 64 diffusion sampling directions with 8 b0 images were acquired with a b-value was 1000 s/mm2. Connectometry analysis was conducted using DSI Studio.

Results: The participants had diagnoses of GAD, MDD, SAD, PTSD, and panic disorder (mean baseline DASS score 30±7.3). There was no significant response differences across treatment arms according to HAM-D scores (p=.11) and HAM-A scores (p=.35). Connectometry analysis revealed increased connectivity in the forceps minor over time that was significantly different in patients compared to controls and correlated with improving DASS scores.

Conclusions: In a preliminary transdiagnostic sample, there was a significant increase in forceps minor connectivity that correlated with treatment response. This white matter region is increasingly emerging as a key circuit involved in treatment response across a wide range of emotional disorders.

Supported By: NIH R01 MH101497 04

Keywords: diffusion imaging, RDoC, treatment response, cognitive behavioral therapy, SSRI

945. The Effect of Brain Shift in Connectomic Targeting for Subcallosal Cingulate Deep Brain Stimulation

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Background: SCC DBS is an experimental therapy for treatment-resistant depression (TRD). Recent advances highlight a “connectomic targeting” approach which relies on precise electrode placement at the intersection of four white matter bundles in the subcallosal area. Brain shift, induced by opening burr holes in the skull, may alter the relative position of the target pathways during surgery. We utilize longitudinal imaging data to evaluate the variance in postoperative electrode location, compared to the planned target location, to quantify the impact of location deviations on requisite WM pathways.

Methods: Brain shift following surgery was assessed on 15 TRD subjects at multiple time-points (preoperative, 24h and 3 weeks postoperative) along the electrode trajectory using anatomical control points, pneumocephalus, electrode location, and track activation changes. Data from the 3 time points were aligned to the stereotactic frame T1 using a rigid body registration.
Results: Significant brain shift was recorded in the frontal-pole, which was accompanied by pneumocephalus. Electrode displacements from planned locations were observed in the anterior-superior direction. Leads implanted in the right hemisphere were generally more displaced than those in the left. Track activation predictions for ventral-striatum connectivity were decreased in both left and right hemispheres, while the frontal-pole connection was increased only in the right hemisphere.

Conclusions: These results demonstrate that brain shift induces electrode displacement and tract activation changes in SCC-DBS. Brain shift may have a significant effect on the precision of SCC targeting requiring reconfirmation of contact selection once shift has subsided.

Supported By: Hope depression research foundation
Keywords: Brain shift, DBS, Subcallosal Cingulate, Treatment Resistant Depression

946. Decreased Occipital Glutathione in Adolescent Depression: A Magnetic Resonance Spectroscopy Study
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Background: Adolescent depression (MDD) is a major public health concern, accompanied by substantial impairment including elevated suicide risk. Recent data point to the role of increased oxidative stress in the pathophysiology of depression. One important marker of oxidative stress is glutathione (GSH) depletion, the brain’s major antioxidant system. Limited research has investigated GSH in vivo in MDD, and no GSH studies have examined depressed adolescents.

Methods: Using 1H-MRS, we compared GSH levels in the occipital cortex of 19 psychotropic medication-free adolescents with MDD and 8 healthy controls (HC). We next examined correlations between GSH and dimensional measures of depression (CDRS-R) and anhedonia (SHAPS) in the full sample. Finally, we investigated whether episode recurrence was linked to GSH levels within the MDD group.

Results: T-tests revealed that the MDD group had significantly lower levels of GSH/water (GSH/w) than HC (.0018 vs .0024, p=.04). In the full sample, there was a significant negative correlation between GSH/w and CDRS-R (r = -.41, p=.04), but not SHAPS. In the MDD group, t-tests showed significantly lower GSH/w in adolescents with recurrent episodes, compared to those with a single episode (.0016 vs .0019, p=.04); however, there were no differences in CDRS-R between groups, suggesting that this difference in GSH is not due to MDD severity.

Conclusions: Findings implicate reduced GSH in adolescent MDD, and suggest a possible link to episode recurrence. Our investigation may provide insight into the early pathogenesis of MDD and help to identify biomarkers of risk.

Supported By: RO1MH095807
Keywords: 1H MRS, Adolescent Depression, Glutathione Depletion

947. Spread of Activity following TMS is Correlated with Intrinsic Resting Connectivity with the Target Region: A Concurrent TMS-fMRI Study

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Background: Transcranial magnetic stimulation (TMS) modulates activity to regions distal to the site of simulation. Concurrent TMS-fMRI represents a technique to directly assess the spread of brain activity following TMS. This spread of activity may depend on individual patterns of functional connectivity.

Methods: In twenty-two participants, resting-state fMRI scans were acquired. This was followed by four ten minute sessions of concurrent TMS-fMRI, each of 50 single pulses of TMS over the left dorsolateral prefrontal cortex. Seed-based connectivity was performed from the baseline resting fMRI scan data (using the TMS target as the seed). The TMS-fMRI data were analyzed using a general linear model to identify TMS-induced changes in brain activity. Correlation between baseline resting state connectivity and TMS-induced change at the individual level was the primary measure of interest.

Results: There was a significant relationship between resting connectivity and TMS induced changes in brain activity (t=2.39, p=0.026). When this relationship was examined at the individual level, five participants did not show significant correlation between TMS induced changes in activity and resting state connectivity, twelve participants showed a positive correlation, and five atypical TMS-fMRI activators showed a negative correlation. The level of correlation was modulated by the extent and direction of activity following TMS.

Conclusions: Our results directly demonstrate that there is a relationship between the change in brain activity in response to TMS and resting connectivity. However, there was substantial individual variability in the response to TMS, which must be considered in clinical work using resting connectivity to predict TMS response.

Supported By: NSERC
Keywords: Transcranial magnetic stimulation, TMS-fMRI, resting state, connectivity, functional MRI

948. Association between Age and Grey Matter Density in Youth with and without Bipolar Disorder

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Background: Few neuroimaging studies examine grey matter (GM) trajectories in youth bipolar disorder (BD), and findings are mixed. A cross-sectional study of 18-75 year old adults compared the correlation between age and GM between BD and healthy control (HC) participants, and reported no differences (Sani et al., 2016; Bipolar Disorders). However,
the BD group consistently had less GM than HC across entire age-range. We investigated the association between age and GM in 13-20 year old adolescents with and without BD.

Methods: T1-weighted images of a sex-matched sample of 44 BD adolescents and 50 HCs were processed using voxel-based morphometry on SPM12. Spherical a priori regions of interest (ROI), motivated by previous adult study, were created from intracranial volume-normalized images to extract grey matter density (GMD) of the posterior cingulate cortex (PCC), right/left cerebellum, and right thalamus. Univariate general linear models examined the association between age and GMD of ROIs.

Results: There was a significant diagnosis-by-age interaction effect on right cerebellum GMD (p=.043, $\eta^2$p=.045). In the HC group only, age was negatively correlated with right cerebellum GMD (p=.006, $\eta^2$p=.147). In examining main effects, BD group had less GMD than HC in the PCC (p=.006, $\eta^2$p=.086) and age was negatively correlated with GMD in PCC (p<.001, $\eta^2$p=.194), right cerebellum (p=.045, $\eta^2$p=.043), and right thalamus (p=.002, $\eta^2$p=.097).

Conclusions: Our results suggest that there may be a putative neurodevelopmental association between BD and cerebellar GMD during adolescence. Longitudinal studies employing repeated measures are warranted to resolve direction of observed associations.

Supported By: Ontario Mental Health Foundation

Keywords: grey matter density, voxel-based morphometry, bipolar disorder, age, adolescents

949. Replicated Aberrant Default Mode Resting State Functional Connectivity in Patients with Remitted Psychotic Depression

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Background: The default mode network (DMN) has been implicated in major depressive disorder (MDD) however there are currently no studies of the DMN in MDD patients with psychotic features who are treated to remission. We hypothesized that such patients would not differ from controls in DMN functional connectivity yet show aberrant functional connectivity between the DMN and other brain regions.

Methods: Resting state functional magnetic resonance imaging (R-fMRI) scans were obtained on a 3T scanner at the Centre for Addiction and Mental Health (CAMH) in a sample of healthy controls (n=39) and patients (n=28) who remitted on a combination of sertraline and olanzapine. Data was processed with the Functional MRI of the Brain (FMRIB) Software Library (FSL 5.0.6), including FMRIB's ICA-based Xnoisefier (FIX). Dual regression was employed and group differences between controls and patients were tested using FSL randomise. All results were family-wise error corrected at p<.05. This analysis was repeated in an independent sample from the University of Pittsburgh Medical Center (UPMC) using 3T scans of healthy controls (n=20) and patients (n=14) who obtained remission with the same medications.

Results: There were no significant within-DMN differences between patients and controls in the CAMH discovery sample. Patients had significantly decreased bilateral insular and sensorimotor functional connectivity with the DMN relative to controls. These findings were replicated in the sample from UPMC.

Conclusions: These aberrant functional connections may serve as a biomarker for diagnosis or targeted treatments. Future research will investigate whether such functional connectivity patterns predict treatment trajectories.

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Keywords: Resting state fMRI, Remitted Major Depressive Disorder (RMD), psychosis phenotype, Antipsychotics, Antidepressants

950. Increased Pet-Detectable Tau Pathologies in Late-Life Depression with Psychosis

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Background: Depression has been identified as a risk factor of Alzheimer’s disease. Common neuropathological changes may underlie these two diseases. In this study, we examined tau and amyloid-β (Aβ) accumulations in the brains of subjects with late-life depression in comparison with healthy controls by using positron emission tomography (PET) with a tau radioligand, [11C]PBB3, and an Aβ radioligand, [11C]PiB.

Methods: Fourteen late-life depression patients (8 patients with psychosis) and 12 age-matched healthy controls were examined by PET with [11C]PBB3 and [11C]PiB, and tau and Aβ depositions were quantified as standardized uptake value ratios for these radioligands. We also examined clinical manifestations of patients by Hamilton Depression Scale and Geriatric Depression Scale for depression symptoms, Mini-Mental State Examination for cognitive functions, and Clinical Dementia Rating for activity of daily living.
Results: There was a trend toward increased tau accumulations in patients with late-life depression compared to healthy controls, while levels of Aβ depositions were equally low in patients and controls. Notably, patients with psychotic symptoms exhibited greater tau loads (p < 0.01) than those without psychotic symptoms. However, tau depositions were not significantly correlated with any of the clinical symptoms examined here.

Conclusions: The current findings implicate tau pathologies in the pathophysiology of late-life depression with psychotic symptoms, indicating a potential therapeutic approach to this disease based on PET-visible pathologies.

Keywords: TAU PROTEIN, Depression, PET, Late Life Depression, Neuroimaging

951. Changes in Resting-State Global Connectivity in LSD-Induced Altered States of Consciousness are Attributable to the 5-HT2A Receptor

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Background: Lysergic acid diethylamide (LSD) is a prototypical psychedelic drug with agonist activity at various serotonin (5-HT) and dopamine receptors. Despite the therapeutic and scientific interest in LSD, the specific receptor contributions in particular to changes in brain connectivity have not been studied yet.

Methods: In a double-blind, randomized, counterbalanced, cross-over study 24 healthy participants received either 1) placebo+placebo, 2) placebo+LSD (100 μg po), or 3) ketanserin - a selective 5-HT2A receptor antagonist (40 mg po)+LSD (100 μg po) in three different sessions. Resting-state fMRI scans were acquired 75 and 300 minutes after the second substance administration. We analyzed resting-state functional connectivity with a data-driven global brain connectivity (GBC) method to facilitate discovery.

Results: LSD administration caused widespread alterations of GBC across cortical and subcortical regions. LSD decreased GBC in fronto-medial and lateral areas, as well as basal ganglia, but increased GBC in the occipital, temporal, and parietal cortex. Similar patterns were found when comparing LSD with ketanserin+LSD. Negligible differences were observed when comparing ketanserin+LSD and placebo.

Conclusions: Results revealed that LSD induces widespread GBC alterations that are predominantly attributable to its agonistic activity onto the 5-HT2A receptor. While LSD reduces connectivity in attention networks, it increased connectivity across sensory areas. Present results inform psychedelics' mechanism of action pinpointing targets of therapeutic value and reinforce use of data-driven neuroimaging methods for pharmacological imaging.

Supported By: Swiss National Science Foundation; Usona Institute; Heffer Research Institute; Swiss Neuromatrix Foundation

Keywords: serotonin 2A receptor, Resting state functional connectivity, BOLD fMRI, Pharmacology

952. Light Therapy Facilitates Thalamo-Cortical Brain Recovery from Mild Traumatic Brain Injury

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Background: Mild traumatic brain injury (mTBI) or “concussion” is often associated with persistent problems with sleep for up to 50% of patients. We hypothesized that regular morning blue light exposure therapy may re-entrain the circadian rhythm and improve sleep, potentially enhancing brain repair and neuropsychological recovery.

Methods: Twenty-eight individuals (15 female; 18-48 years) with a documented mTBI during the preceding 18 months underwent a comprehensive neuropsychological assessment and multi-modal neuroimaging. Participants completed 6-weeks of daily morning light exposure (30 min/day) with a light device fitted with blue (n=14) or amber wavelength (placebo; n=14) diodes, and returned for follow-up assessment and imaging.

Results: Blue light exposure led to an earlier bedtime and rise time, lower daytime sleepiness, and improved balance compared to placebo light (p<.05). Structural magnetic resonance imaging (MRI) showed that active blue-light treatment was associated with increased volume of the pulvinar nucleus bilaterally (p<.05, FWE corrected), while no difference was observed for amber placebo. Blue light was also associated with increased functional connectivity and greater integrity of white matter axonal pathways connecting the pulvinar to parietal regions compared to placebo (p<.05, FWE corrected). Changes in functional and structural connectivity correlated with improved neurocognitive performance.

Conclusions: Daily morning exposure to blue-wavelength light for 6-weeks led to improved sleep and associated alterations in thalamo-cortical structure, connectivity, and function compared to amber placebo light exposure. These preliminary findings raise the possibility that blue-light treatment may provide a novel method for improving recovery from some aspects of mTBI.

Supported By: USAMRAA grant W81XWH-11-1-0056

Keywords: Light Therapy, Traumatic Brain Injury, MRI, DTI, Functional Connectivity

953. Reciprocal Disruptions in Cortico-thalamic and Hippocampal Connectivity in Youth at Genetic High Risk for Psychosis

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Background: Copy number variants (CNVs) that are highly penetrant for psychosis -like the 22q11.2 deletion - offer remarkable translational potential, as the same genetic defect observed in human patients can be modeled in animals and in culture. Here we present novel data from a prospective study of a large cohort of youth with 22q11.2 deletions (22q11DS), in which we interrogated candidate neural systems implicated in schizophrenia (i.e., altered functional connectivity within subcortical-cortical circuits) in relation to the development of psychotic symptoms.

Methods: We acquired structured clinical interviews, high-resolution T1-weighted structural magnetic resonance imaging (MRI) scans and resting-state functional MRI scans in 42 youth with 22q11.2 deletions and 40 demographically matched controls. A subset was followed longitudinally for one year.

Results: Functional connectivity (FC) analyses revealed that 22q11DS patients showed thalamic hyper-connectivity with auditory cortex, but under-connectivity with striatal and cerebellar regions, consistent with patterns recently observed in CHR youth who subsequently developed overt psychosis. In contrast, inputs to hippocampal cortex were significantly reduced in 22q11DS relative to controls, such that there was increased thalamic coupling with sensorimotor networks and decreased coupling with prefrontal-hippocampal regions in 22q11DS patients. Finally, longitudinal data indicated that changes in thalamo-cortical connectivity over time predicted the development of prodromal psychotic symptoms in 22q11DS patients.

Conclusions: Reciprocal disruptions of hippocampal and thalamic circuitry in 22q11.2 deletion carriers, implicate large-scale network disruptions that converge with those observed in idiopathic psychosis and show direct parallels to work in mouse models. Further, severity of these disruptions may predict symptom development over time.

Supported By: NIH grant U54 EB040203; NIMH Grant RO1 MH085953

Keywords: copy number variant, Functional connectivity, psychosis-proneness, Thalamocortical circuitry, At-Risk Youth

954. Higher Order Thalamic Nuclei Resting Network Connectivity in First Episode Schizophrenia and Major Depressive Disorder

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Background: The pulvinar and the mediodorsal (MDN) nuclei of the thalamus are higher order nuclei which have been implicated in directed effort and corollary discharge systems. We used a seed-based resting fMRI analysis to examine the functional connectivity of the pulvinar and MDN in schizophrenia and major depressive disorder (MDD).

Methods: Resting fMRI data were acquired from 24 schizophrenic patients (SZ), 24 MDD patients, and 24 healthy controls matched for age and illness duration. We performed seed-based connectivity analyses with seeds in bilateral pulvinar and MDN, covarying for gender and smoking (p < 0.05, FWE-corrected; SPM8).

Results: SZ had less connectivity than controls between left pulvinar and precuneus, left ventral-lateral prefrontal cortex (vPFC), and superior and medial-frontal regions, between right pulvinar and right frontal pole, and greater connectivity between right MDN and left dorsolateral prefrontal cortex (dPFC). SZ had less connectivity than MDD between the left pulvinar and ventral anterior cingulate (vACC), left vPFC, anterior insula, posterior cingulate cortex (PCC), and right hippocampus, between the right pulvinar and right PCC, and between the right MDN and right dorsal anterior cingulate (dACC).

Conclusions: This is the first study to measure the functional connectivity to the higher order nuclei of the thalamus in both SZ and MDD. We observed less connectivity in SZ than MDD between pulvinar and emotional encoding regions (vACC and vPFC), a directed effort region (PCC), and a region involved in representation and salience (anterior insula), and between MDN and a directed effort region (right dACC).

Supported By: Canadian Institutes of Health Research (CIHR)

Keywords: Schizophrenia, Major Depressive Disorder (MDD), Resting state functional connectivity, pulvinar thalamic nucleus, mediodorsal thalamic nucleus

955. Striatal Phosphodiesterase 10A and Medial Prefrontal Cortical Thickness in Patients with Schizophrenia: A PET and MRI Study

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Background: The enzyme phosphodiesterase 10A (PDE10A) is abundant in striatal medium spiny neurons, where it regulates postsynaptic dopamine signaling. It has been implicated in the pathophysiology of schizophrenia in animal models and is investigated as a potential pharmacological target. Thinning of the prefrontal cortex is common in schizophrenia, but how this relates to PDE10A expression is unknown. Here we compared, for the first time, the striatal non-displaceable binding potential (BPND) of the new validated PDE10A ligand [11C]Lu AE92686 between patients with schizophrenia and healthy controls. Furthermore we aimed to assess the correlation of PDE10A BPND to cortical thickness.

Methods: Sixteen healthy male controls and 10 male patients with schizophrenia treated with clozapine, olanzapine or quetiapine were investigated with positron emission tomography (PET) and magnetic resonance imaging (MRI). Striatal binding potential (BPND) of [11C]Lu AE92686 was acquired through dynamic PET scans and cortical thickness by structural MRI. Clinical assessments of symptoms and cognitive function were performed and antipsychotic dosage recorded.
Results: Patients with schizophrenia had significantly lower BPND of [11C]Lu AE92686 in striatum (p = 0.003) than controls. The striatal BPND significantly correlated to cortical thickness in the anterior cingulate cortex and superior frontal gyrus in both patients with schizophrenia and healthy controls. No significant correlation was observed between BPND for [11 C]Lu AE92686 in striatum and age, schizophrenia symptoms, antipsychotic dosage, coffee consumption, smoking, illness duration, or cognitive function in the patients.

Conclusions: In conclusion, PDE10A may be important for functioning in striato-cortical interaction and in the pathophysiology of schizophrenia.

Supported By: Söderström-Königska Foundation
Keywords: Schizophrenia, Positron Emission Tomography, Magnetic resonance imaging, striatum, Cortical Thickness

956. System-Specific Alterations of Brain Connectivity in Psychosis
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Background: Psychotic disorders are associated with alterations in the functional connectivity of brain networks. In this study we tested the hypothesis that community structure of higher order cognitive networks is affected to a greater extent than more basic sensory and motor networks in psychosis.

Methods: Resting state fMRI scans were acquired from 77 people with a psychotic disorder and 47 healthy controls. The brain was divided into 723 regions of interest. Each region was assigned to one of 7 a priori networks that had been previously identified by a data-driven parcellation of a large sample of healthy people. Based on the a priori structure, modularity was computed for three graphs: the full network; the subset of regions in primary sensory and motor networks; and the subset of regions in fronto-parietal, dorsal attention, and default mode networks. Modularity was reported from correlation matrices thresholded at values R = 0, 0.05,..., 0.70.

Results: For the fronto-parietal/attention/default sub-network, modularity was 8 percent lower in the psychosis group at a threshold range of 0.35 <= R <= 0.7 (p<0.05). However, for the full network structure and the sensorimotor sub-network, no differences in modularity were observed.

Conclusions: The community structure of basic sensory and motor networks was normal appearing in psychosis. However, there was reduced functional segregation in psychosis specific to higher-order cognitive networks comprising fronto-parietal, dorsal attention, and default mode networks.

Supported By: NIH R01MH102266
Keywords: Psychosis, Functional connectivity, Graph theory

957. Neurite Orientation Dispersion and Density Imaging (NODDI) of the Prefrontal Cortex in Psychosis
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Background: Individuals with psychosis exhibit changes in prefrontal cortex (PFC) microstructure, including reduced spine density and shorter total dendritic length. However, in vivo evidence of altered PFC microstructure is lacking. We used neurite orientation dispersion and density imaging (NODDI) to investigate cortical microcircuitry in vivo in individuals with psychosis.

Methods: Multishell diffusion imaging and high resolution anatomical T1-weighted imaging was acquired on 67 individuals with a psychotic disorder and 47 healthy control subjects. Using the NODDI model, neurite orientation dispersion index (ODI), a putative marker of dendritic structure and complexity, was calculated and compared between healthy controls and individuals with psychosis using region-of-interest (ROI) and voxel-wise approaches.

Results: Multivariate ANOVA of the ROI results revealed a significant interaction between PFC sub-region (medial, lateral, and orbitofrontal) and group (p=.002). Follow-up analyses showed that psychosis patients exhibited reduced ODI in the medial PFC of both the left (p=.003) and right (p=.002) hemispheres. Voxel-wise ANCOVA analysis performed using Biological parametric mapping (BPM) to control for voxel-wise grey matter volume showed significant differences between healthy subjects and psychosis patients in the anterior cingulate and right dorsolateral PFC (voxel-wise results cluster-level corrected p<.001).

Conclusions: Dendritic complexity in anterior cingulate and dorsolateral PFC is reduced in psychosis. Results are consistent with post-mortem findings of reduced dendritic spine density and shorter total dendritic length in the PFC in psychosis. Further work is required to establish the functional consequences of reduced PFC neurite complexity, and determine the effects of antipsychotic medication of neurite complexity measured in vivo.

Supported By: 5R01MH102266
Keywords: PFC, Psychosis, neurite outgrowth, diffusion imaging

958. Characterizing Structural and Functional Brain Connectivity Changes in African Americans with Schizophrenia and Affective Psychosis
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Background: Degeneration in the structural and functional connections between brain regions plays a principal role in the pathophysiology of psychosis. Advances in diffusion weighted imaging and resting-state functional MRI yield an unprecedented capability to characterize simultaneous alterations in structural and functional connectivity in relation to the psychosis phenotype. Recent evidence indicates that
connectivity abnormalities emerge early and develop throughout duration of illness, suggesting the clinical utility of neuroimaging approaches across the psychosis continuum.

**Methods:** In order to more fully characterize psychotic dysconnectivity in a traditionally understudied population, structural and functional connectivity patterns in African Americans with schizophrenia, psychotic bipolar disorder, and other affective psychoses (n=78) were compared to those of a demographically matched control group (n=83). Neuroimaging data were collected and processed according to the next-generation acquisition and analysis guidelines developed by the Human Connectome Project. Type I error was corrected using non-parametric permutation based methods.

**Results:** Diagnostic and dimensional indices of psychosis were quantified in relation to data-driven functional and probabilistic structural tractography-based connectivity. Results indicate that data-driven methods can be readily combined in a multivariate way to map concurrent structural and functional alterations in association with psychotic symptom severity.

**Conclusions:** This study is among the first to investigate connectivity characteristics in an exclusively African American patient population, reducing the genetic heterogeneity typically associated with studies that include diverse ethnic groups. Results suggest that structural and functional connectivity patterns can be combined to jointly yield markers of psychotic severity, which can be iteratively refined to serve as a multivariate marker of psychotic illness.

**Supported By:** National Institutes of Health

**Keywords:** African Americans, Resting state functional connectivity, Structural connectivity, Schizophrenia, Bipolar disorder

**Results:** We observe reduced cortical thickness indices in both illnesses, though less pronounced in bipolar disorder. While schizophrenia (n=226) was associated with wide-spread surface area reductions, bipolar disorder (n=227) and healthy comparison subjects (n=370) did not differ. We replicate earlier reports that head motion (estimated from time-series data) influences surface area and cortical thickness measurements and demonstrate that motion influences a portion, but not all, of the observed between-group structural differences. When conditioning on global surface area or cortical thickness indices, between-group neuroanatomic effects were largely ablated.

**Conclusions:** While head motion is significantly associated with cortical thickness and surface area, it does not appear to account for all of the between-group differences. By covarying global cortical thickness and surface area measurement, we find little evidence for neuroanatomic specificity in affective and psychotic disorders. Although we are not the first to report the non-specificity of structural brain changes these illnesses, our findings are contrary to the vast majority of published reports on the topic.

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**Keywords:** Schizophrenia, Bipolar Disorder, Neuroanatomy, Neuroimaging, Structural MRI

**960. Schizophrenia Exhibits Bi-Directional Brain-Wide Alterations in Cortico-Striato-Cerebellar Circuits**

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**Background:** Distributed neural dysconnectivity is considered a hallmark feature of schizophrenia, yet a tension exists between studies pinpointing focal disruptions versus those implicating brain-wide disturbances. The cerebellum and the striatum communicate reciprocally with the thalamus and cerebral cortex through monosynaptic and polysynaptic connections, forming cortico-striatal-thalamic-cerebellar (CSTC) functional pathways that may be sensitive to brain-wide dysconnectivity in schizophrenia. It remains unknown if the same brain-wide pattern of alterations persists across CSTC systems, or if specific alterations exist along key functional elements of these networks.

**Methods:** We characterized whole-brain cerebellar and striatal connectivity using resting-state functional magnetic resonance imaging in 159 patients with chronic schizophrenia and 162 matched controls, along each major cerebellar and striatal functional subdivision. Functional subdivisions were defined using both an a priori functional parcellation and data-driven clustering of voxelwise connectivity. Parallel independent analyses were conducted for the cerebellum and the striatum and nonparametrically tested.

**Results:** Results revealed consistent brain-wide bi-directional alterations for both the cerebellum and striatum in patients...
relative to controls, marked by hyper-connectivity with bilateral sensory-motor cortices and hypo-connectivity with association cortex. Similar to previous findings of thalamic dysconnectivity in schizophrenia, these alterations were more pronounced along the executive subdivisions of these systems.

Conclusions: Previous studies have proposed that the highly replicated disruption in thalamic functional connectivity may be a hallmark of schizophrenia. Our results implicate a consistent motif of bi-directional brain-wide alterations in cortico-striato-cerebellar systems, calling into question accounts of exclusively focal disturbances. Rather, the disruption appears to be generalized across functional brain-wide circuits.

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Keywords: Schizophrenia, neural circuits, Resting state fMRI, Cerebellum, striatum

961. Incentives to Perform: The Effects of Reward on Working Memory

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Background: Incentives are powerful in motivated, goal-directed behavior. Behavioral research suggests that rewarding, and loss-avoiding, incentives boost cognitive performance. Little is known about how incentives influence neural cognitive control circuits. fMRI was used to examine trial-by-trial behavior and BOLD signal in a spatial working memory (WM) task under rewarding and loss-avoiding conditions in healthy human adults.

Methods: 31 healthy adults performed a WM task under the influence of monetary incentives in the fMRI scanner. As part of a larger task design, WM trials were performed with the possibility for monetary reward or loss at the start of each trial. Images were collected in a 3T scanner using multi-band sequences and parameters consistent with protocols from the Human Connectome Project (HCP). Pre-processing protocols were consistent with the HCP pipeline. Permutated statistics were used to examine fMRI results.

Results: WM accuracy improved in trials that provided the possibility for monetary reward or loss (p<0.001 for both). Rewarding cues at the start of WM trials activated the ventral striatum, midline thalamus, bed nucleus of the stria terminalis (BNST), temporal lobe cortex and occipital cortex (all p<0.05). Cues for loss avoidance at the start of WM trials activated the BNST, parietal cortex, primary motor cortex, and occipital cortex (all p<0.05).

Conclusions: Spatial WM performance improved in response to rewarding and loss-avoiding incentives. Distinct patterns of neural activation appeared to encode rewarding and loss-avoiding cues at the start of a WM task. Future work will involve connectivity analyses, and translation to psychiatric patient populations.

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Keywords: BOLD fMRI, Reward, Working memory, Incentive motivation, Schizophrenia


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Background: Converging lines of evidence from postmortem, neuroimaging and genetic studies suggest the presence of abnormalities in synaptic structure and function in schizophrenia (SCZ). The development of UCB-J, a novel Positron Emission Tomography (PET) ligand with high specificity for synaptic vesicle glycoproteins 2A (SV2A), offers a unique opportunity to image synaptic density in-vivo in the human brain. The aim of the study was to measure synaptic density in SCZ using [11C]UCB-J and High Resolution Research Tomography (HRRT); and to relate synaptic density to disease phenomena and electrophysiological (EEG) correlates of memory.

Methods: Chronic SCZ patients and healthy controls underwent PET imaging using [11C]UCB-J. [11C]UCB-J binding (VT) was compared between the two groups. EEG data were acquired while subjects participated in a modified verbal memory task.

Results: Relative to age- and gender-matched controls, SCZ patients (n=6) showed global reductions (effect size, d=0.87) in [11C]UCB-J (VT) binding with greatest group differences in the amygdala. Theta activity during the encoding was highly correlated with [11C]UCB-J VT in DLPFC (p<0.001) and posterior cingulate (p=0.042).

Conclusions: These data show that synaptic density is decreased in-vivo in SCZ. Synaptic density was found to correlate with task-related theta-band power in brain regions relevant to encoding.

Supported By: Dana Foundation: David Mahoney Neuroimaging Program, Thomas P. Detre Fellowship Awards in Translational Neuroscience Research in Psychiatry,

Keywords: Schizophrenia, PET imaging, synapses, verbal memory

963. Linking Time and Space to Identify Neural Mechanisms of Semantic Processing Impairments in Schizophrenia: An ERP-fMRI “Fusion” Study

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Background: Language processing in schizophrenia (SZ) is characterized by imprecise associations within semantic networks, revealed experimentally by reduced amplitude of the N400 event-related potential (ERP) component elicited by semantic violations. Language paradigms using fMRI with SZ patients have revealed abnormal modulation and impaired connectivity across a wide range of cortical structures, while underlying neuroanatomical links to ERP findings remain unknown.

Methods: SZ patients (n=24) and healthy control subjects (HC; n=24) performed a picture-word semantic priming task in separate ERP and fMRI sessions. In the priming task, subjects indicated whether a word was a semantic match or non-match relative to the preceding picture. Data were analyzed using joint independent components analysis (JICA) to identify brain regions associated with the ERP N400 component. JICA identified regions were included in a parametric modulation analysis, to identify the effect of semantic relatedness on functional connectivity.

Results: JICA identified an ERP-fMRI “fused” component that captured the N400 component and associated bilateral fMRI activations in visual, cingulate, posterior parietal, superior temporal, medial and orbitofrontal cortices. The component scores associated with this fused JICA component were reduced in SZ relative to HC (p<0.001). SZ patients showed reduced and diffuse N400-related activation, except for medial frontal regions, where activity was enhanced. Functional connectivity increased between orbitofrontal and visual cortices with semantic relatedness in SZ, but decreased in HC subjects.

Conclusions: These findings are consistent with an overly broad spread of semantic activation in SZ, perhaps owing to inefficient (increased) frontal activity and connectivity in response to semantic violations.

Supported By: NIMH MH058262; VA 101 CX000497

Keywords: Schizophrenia, SEMANTIC ASSOCIATION, Event Related Potentials, fMRI, Independent Components Analysis

965. Investigating Brain Structure Across Bipolar Disorder Subtypes: Findings from the Psychosis Affective Research Domain Intermediate Phenotypes (PARDIP) Study

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Background: Bipolar 1 disorder is characterized by severe mood changes meeting DSM criteria for major depressive disorder and mania presented with (BPP) or without psychotic features (BPNP). One small, cross-sectional study showed greater cortical thinning in bilateral pre-frontal cortex and left anterior cingulate which was more pronounced in subjects with a psychosis history. In an ongoing study, we examined our hypothesis that BPP would show greater cortical thinning compared to BPNP.

Methods: Subjects included individuals with BPP (n=46), BPNP (n=35) and healthy controls (HC, n=51) as part of the ongoing Psychosis Affective Research Domain Intermediate Phenotypes study. Cortical thickness measures were extracted from T1 structural MRI scans using Freesurfer 5.3. Group-wise thickness 2.2mm, b-value 1000 s/mm2, 5 b0 images). Motion and eddy current correction were performed with FSL EDDY. Diffusion data were reconstructed in MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function, with a sampling length ratio of 1.25. Group diffusion connectometry was performed to examine the relationship between connectivity and clinical response after six weeks of treatment with multiple regression analyses using age and sex as covariates. Local connectomes were tracked using a deterministic fiber tracking algorithm, with seed density of 100 seeds/mm2, 2.3 t-threshold, and 50mm length threshold, all tracks from bootstrap resampling were included. A total of 2000 randomized permutations were applied to obtain the null distribution of the track length.

Results: Connectometry analysis indicated that greater connectivity in the corpus callosum, external capsule and cerebellar peduncle at baseline is related to better treatment response after six weeks of treatment.

Conclusions: Our results suggest a relationship between white matter integrity and response to antipsychotic medications. Future studies investigating the pathophysiological mechanisms underlying white matter alterations will be important for targeted drug development.

Supported By: NIMH R01, K23

Keywords: white matter integrity, Schizophrenia, Treatment Response, Diffusion Tensor Imaging (DTI)

964. White Matter Integrity, Measured with Diffusion Connectometry, in Unmedicated Patients with Schizophrenia and Response to Antipsychotic Treatment

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Background: A number of studies have reported decreased white matter integrity in patients with schizophrenia, but little is known the relationship between white matter alterations and response to antipsychotic treatment.

Methods: We enrolled 30 unmedicated patients with schizophrenia in a six week longitudinal trial with risperidone. Symptoms were assessed with the Brief Psychiatric Rating Scale. We obtained diffusion weighted images before treatment initiation. 30 diffusion directions were acquired twice and concatenated (in plane resolution 2.2mm, slice thickness 2.2mm, b-value 1000 s/mm2, 5 b0 images). Motion and eddy current correction were performed with FSL EDDY. Diffusion data were reconstructed in MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function, with a sampling length ratio of 1.25. Group diffusion connectometry was performed to examine the relationship between connectivity and clinical response after six weeks of treatment with multiple regression analyses using age and sex as covariates. Local connectomes were tracked using a deterministic fiber tracking algorithm, with seed density of 100 seeds/mm2, 2.3 t-threshold, and 50mm length threshold, all tracks from bootstrap resampling were included. A total of 2000 randomized permutations were applied to obtain the null distribution of the track length.

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Conclusions: Our results suggest a relationship between white matter integrity and response to antipsychotic medications. Future studies investigating the pathophysiological mechanisms underlying white matter alterations will be important for targeted drug development.

Supported By: NIMH R01, K23

Keywords: white matter integrity, Schizophrenia, Treatment Response, Diffusion Tensor Imaging (DTI)
966. Cortical Gray-White Matter Contrast Underlying Negative Symptoms and Verbal Memory in First Episode Psychosis

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Background: Negative symptoms following a first episode of psychosis (FEP) are an unmet therapeutic need, tightly linked to poor verbal memory (VM). This study uses a novel metric of gray-white matter ratio (GWR) to probe longitudinal properties of tissue contrast and their interaction with negative symptoms, as well as associations with VM.

Methods: T1-weighted images were acquired at three timepoints for 117 FEP patients (ages 18-35; N = 89 with longitudinal data). Images were processed using CIVET (Version 2.1). Two additional surfaces were generated, sampling 1mm inward (-1mm) and outward (+1mm) in relation to the white matter surface. GWR was calculated by dividing the intensity of the -1mm point by the corresponding +1mm point. Linear mixed models tested for an interaction between timepoint and negative symptoms, namely amotivation (AM) and affective (AFF) symptom dimensions. GWR correlates of VM were investigated cross-sectionally with a general linear model.

Results: Regions encompassing inferior temporal, subgenual cingulate, medial prefrontal cortex, supplementary motor area, and parietal cortex were associated with AM and AFF dimensions across time in FEP (p’s<0.05, corrected). A significant positive association between GWR and VM was found within the right ventrolateral prefrontal cortex (r=0.32, p=0.0005).

Conclusions: This study demonstrates patterns of GWR changes over time within FEP patients with respect to negative symptoms, as well as a positive relationship with VM in the right homolog of Broca’s area. GWR arguably indexes biophysical properties of underlying tissue and may be more sensitive in detecting subtle clinical differences compared to conventional cortical thickness measures.

Supported By: CIHR #68861

Keywords: First Episode Psychosis, Negative Symptoms, verbal memory, Structural MRI, Longitudinal Brain Imaging

967. Using Coordinate-Based Meta-Analyses to Explore Structural Imaging Genetics

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Background: Since its introduction to psychiatric research, imaging genetics has become a highly popular approach in the field of schizophrenia research. A frequently reported finding is that the effects of various common genetic variations are associated with structural changes in brain regions that are known to be affected in schizophrenia. Moreover, given that the diagnosis of schizophrenia is based on a constellation of clinical symptoms, rather than a common pathomechanism, a structural endophenotype might be easier to delineate, when recurring to biological criteria rather than diagnosis. Coordinate-based meta-analyses are powerful tools to potentially objectify these hypotheses, capitalizing on the wealth of the published literature in this field.

Methods: We then used the anatomical likelihood estimation (ALE) algorithm on a total of 30 imaging genetics studies on schizophrenia variants. To investigate, whether analyses based on gene ontology would increase the convergence of results, we used the STRING data base to group the studies accordingly.

Results: We did not retrieve significant results for most contrasts, however, our analysis enrolling studies on genotype X diagnosis-interaction yielded two clusters in the left temporal lobe and the medial orbitofrontal cortex.

Conclusions: While our lack of significant findings for most contrasts applied should urge a more cautious interpretation of the results of individual imaging genetics studies, we were able to provide the first meta-analytical evidence for a convergence of results in imaging genetics using unrestricted inference spaces. Our significant findings for gene X diagnosis-interactions provide first hints that schizophrenia might be a more biologically valid entity than commonly perceived.

Keywords: Imaging genetics, Schizophrenia, Neuroanatomy

968. Reciprocal Disruptions in Cortico-Thalamic and Hippocampal Resting-State Functional Connectivity in Youth with 22q11 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (22q11DS) is a genotype with high penetrance for schizophrenia spectrum disorders. Study of individuals with 22q11DS therefore provides an important causal window into the relationship between the genetic, neural, and behavioral correlates of schizophrenia. Resting-state fMRI Studies in schizophrenia have consistently revealed thalamic and hippocampal neural dysconnectivity. It remains unknown if similar effects can be observed in 22q11DS.

Methods: A sample of youth with 22q11DS (n=42) and demographically matched healthy controls (n=39) were recruited and evaluated for psychotic symptoms. Neuroimaging data were acquired via single-band protocols but analyzed in line with methods provided by the Human Connectome Project (HCP). We computed functional relationships between individual-specific anatomically-defined thalamic and hippocampal seeds and all gray matter vertices in CIFTI grayordinate space. Whole-brain type 1 error protection was achieved through nonparametric permutation-based methods.

Results: 22q11DS patients displayed reciprocal disruptions in thalamic and hippocampal functional connectivity relative to controls. Thalamic-cortical coupling was increased 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: Thalamic and hippocampal dysconnectivity observed in 22q11DS suggest that high genetic risk for psychosis is linked with disruptions in large-scale cortico-subcortical networks, similar to those reported in schizophrenia and in pharmacological models of psychosis. These effects highlight the translational importance of genetic deletion syndromes for informing mechanisms underlying neural disruptions observed in idiopathic schizophrenia.

Keywords: 22q11 Deletion Syndrome, Schizophrenia, Thalamus, Hippocampus, Resting state functional connectivity

970. Binge Drinking Associated with Hippocampal Structural and Functional Abnormalities in Adults with a History of Childhood Adversity

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Background: Although both exposure to early life adversity and alcoholism have been associated with abnormalities in hippocampal structure and function, there are no published studies assessing whether heavy episodic drinking (HED) and early life adversity in adults interact to predict differences in hippocampal volume and intrinsic functional connectivity, the purpose of the current study.

Methods: Multiple regression tests were employed to compare age and gender adjusted Childhood Trauma Questionnaire (CTQ) total scores between 35 HED participants and 22 light or non-drinking (LND) adult subjects recruited from a community clinic in Cape Town. For a subset of 30 participants (HED=19, LND=11), hippocampal volumes were extracted from T1 scans using FreeSurfer (v. 5.3), and intrinsic functional connectivity BOLD data processed with AFNI.

Results: No differences were observed between the HED and LND groups in CTQ scores or hippocampal volumes. Nevertheless, in the HED group higher CTQ total scores predicted smaller left hippocampi (Spearman rho=-0.586, p < 0.01 vs. rho=0.296, p > 0.1 for LND) and increased functional connectivity between the bilateral hippocampus and clusters in the right posterior cingulate cortex and left inferior parietal cortex (FWE corrected, voxel alpha=0.005, cluster extent=29 3mm3 voxels).
Conclusions: We present evidence that the structural integrity and intrinsic function of the hippocampus is compromised as a function of early life adversity, but only in individuals who binge drink. Our findings suggest a possibly synergistic effect of alcohol binges on early stress exposure brain sequelae.

Supported By: South African National Research Foundation, South African Medical Research Council

Keywords: Alcohol, Resting state functional connectivity, Hippocampal Volume, Childhood Trauma

971. Alcohol Use in Adolescents is Related to Disrupted Emotional Neurocircuitry Responsiveness

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Background: Epidemiological data suggests that the lifetime prevalence of Alcohol Use Disorder (AUD) is 30%. Nearly half of all adults with AUD begin drinking alcohol as adolescents. Although mouse studies show that amygdala inhibition reduces anxiety behaviors and alcohol seeking during alcohol withdrawal, human studies of amygdala functioning in alcohol use have yielded mixed results. This preliminary study uses an affective stroop task to investigate emotional neurocircuitry function in adolescents with a history of alcohol use.

Methods: Forty-eight 14-18 year old youths recruited from a residential treatment facility and the surrounding community completed an affective stroop task during fMRI scanning. The affective stroop task allows for an assessment of regulation of responsiveness to emotional distractors as a function of an individual's ability to recruit regions involved in top down attention. Alcohol use history was assessed using the Alcohol Use Disorder Identification Test (AUDIT).

Results: A 3 (Emotion: Negative, Neutral, Positive) x 3 (Task: Congruent, Incongruent, View) ANCOVA with AUDIT scores as a covariate was conducted. This analysis revealed a Task x Covariate interaction in the ventromedial prefrontal cortex, as well as significant 3-way interactions in the amygdala and insula.

Conclusions: These data suggest that there is impaired functioning of the neurocircuitry involving emotion processing in adolescents with a history of alcohol use. Moreover, these disruptions seem to be related to level of alcohol use in adolescents. However, alcohol use in adolescents is often comorbid with ADHD and/or Disruptive Behavior Disorders. Future work should examine the neural relationships between these disorders and alcohol use.

Supported By: Boys Town National Research Hospital

Keywords: fMRI, Alcohol, Emotion, Adolescence

972. Nucleus Accumbens Reactivity and Connectivity to Reward in Binge Drinkers

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Background: Dysfunctional brain reward circuitry is implicated in Alcohol Use Disorder (AUD). Individuals who binge drink are at higher risk for developing AUD and may also exhibit disrupted brain reward reactivity, although this has yet to be tested. We hypothesized that Binge drinkers would differ from Non-Binge drinkers in their neural reactivity and connectivity to a monetary reward, particularly in the nucleus accumbens (NAcc).

Methods: Twenty-seven healthy Binge drinkers and 24 healthy Non-Binge drinkers – none meeting AUD criteria – completed a reward-guessing game, the “Doors” task, during fMRI. Given our a priori hypotheses, we extracted activation from anatomically-based NAcc regions of interest to examine reactivity to reward (wins versus losses) and functional connectivity to the prefrontal cortex to reward.

Results: Compared to Non-Binge drinkers, the Binge drinker group exhibited greater activation in both right and the left NAcc during reward. The Binge drinker group also had less functional connectivity between the NAcc and dorsal anterior cingulate (dACC) during reward compared to the Non-Binge drinker group (FWE small-volume corrected).

Conclusions: Our results provide preliminary evidence that Binge drinkers have greater NAcc responding to rewards, which is consistent with the broader AUD literature and suggests that aberrant reward reactivity may precede disorder onset. In addition, less connectivity between the NAcc and dACC in Binge drinkers may reflect deficient regulation of the heightened responses to rewards. This profile of reward brain circuitry could represent neural correlates of vulnerability for the subsequent development of AUD in this at-risk group.

Supported By: NIDA

Keywords: Alcohol, dACC, BOLD fMRI, Nucleus Accumbens, Reward

973. Imaging Nociceptive Opioid Peptide Receptors in Humans with Alcohol Use Disorders

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Background: The neuropeptide transmitter nociceptin that binds to the nociceptor/ orphanin FQ peptide (NOP) receptor is a core component of the brain’s anti-stress system. Nociceptin exerts its anti-stress effect by counteracting the functions of corticotrophin releasing factor, the primary stress-mediating neuropeptide in the brain. Basic studies have shown that the activation of NOP receptors by nociceptin blunt the reinforcing and motivational effects of alcohol on a range of addictive behaviors. Proof-of-concept studies in humans also suggest a role of NOP antagonists...
in the treatment of alcohol use disorders (AUD). Thus, it is of high interest to measure the in vivo status of NOP receptors in AUD.

**Methods:** In vivo binding to NOP receptors was measured with [11C]NOP-1A and PET in 15 alcoholics and 15 controls matched for age, gender, and smoking status (HC). Alcoholics with no comorbid psychiatric, medical, or drug abuse disorders were scanned following two weeks of outpatient monitored abstinence (confirmed with 3x/week urine ETG/ETS testing). [11C]NOP-1A distribution volume (VT) in regions of interest (including the amygdala, hippocampus, midbrain, striatal and prefrontal cortical subdivisions) were measured with kinetic analysis using the arterial input function.

**Results:** No group differences were noted in [11C]NOP-1A plasma clearance or free fraction. Regional [11C]NOP-1A VT in AUD was not significantly different compared to HC (linear mixed model, diagnosis, p=0.90; region, p <0.001). [11C]NOP-1A VT was not correlated with any of the clinical measures, including duration and severity of AUD, or anxiety or depressive symptoms.

**Conclusions:** These results do not support alterations in NOP receptors in AUD

**Supported By:** NIAAA (R01 AA025247)

**Keywords:** PET, Noceptive opioid peptide, Alcohol Use Disorder, Addiction, Stress

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974. Dysregulation of Hypothalamic-Pituitary-Adrenal Axis and Sympathoadrenergic System is Associated with Posttraumatic Stress Disorder in Combat Veterans

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**Background:** PTSD is associated with abnormalities in central and peripheral sympathetic-adrenomedullary (SAM) system, hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenocortical (HPA) axes. Yet, few studies investigated potential dysregulation in combat veterans with PTSD. We examined SAM and HPG/HPA function in 10 veterans with PTSD, 10 trauma-exposed (TE) veterans without PTSD, and 10 unexposed (UE).

**Methods:** Participants were 18–60 years, male treatment-seeking veterans who fulfilled DSM-IV criteria for PTSD - Clinician Administered PTSD Scale (CAPS) score ≥50. TE controls experienced at least one potentially traumatic event with CAPS ≤15. TE and UE had no history of PTSD or current DSM-IV Axis-I psychopathology. Serum HPA/HPG hormones [Cortisol (CORT), dehydroepiandrosterone-sulphate (DHEA-S), Testosterone (TEST)] and plasma catecholamines (E,NE) measured by immunoassay. Statistical significance (p<0.05) by unpaired-t-test.

**Results:** Relative to controls, veterans with PTSD exhibited significant alterations in basal levels of all SAM and HPA hormones assessed, but not HPG. E and NE were elevated in PTSD (E 1.0 ±0.4; NE 3.1±0.5) vs. TE (E 0.46 ±0.1; NE 1.5±0.4) and UE (E 0.32 ±0.1; NE 1.3±0.4). CORT was lower in PTSD (309.8±55.9) vs TE (399.3±84.2) and UE (463.8±102.8). DHEA-S levels were highest in TE (12.6±2.0), followed by PTSD (7.6±3.7), and lowest in UE (4.9±1.1). TEST trended toward higher values (16.5±3.1) in TE, but did not reach significance compared to PTSD (15.2±5.7) or UE (10.6±2.1).

**Conclusions:** Combat-related PTSD is associated with high circulating levels of E, NE, moderately elevated DHEA-S, but low cortisol. These findings are in accord with data suggesting pronounced dysregulation of SAM and HPA axis activity in veterans with PTSD.

**Supported By:** Defence Research & Development Canada

**Keywords:** Catecholamines, Cortisol, Testosterone, DHEA - Dehydroepiandrosterone, PTSD - Posttraumatic Stress Disorder

975. Circulating PACAP is a Biomarker for Anxiety Disorders in Females

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**Background:** Pituitary adenylate cyclase activating polypeptide (PACAP) is a neuropeptide and hormone 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, and PACAP’s role in stress response, we hypothesize that circulating PACAP will correlate with any anxiety disorder diagnosis.

**Methods:** Serum samples from 215 adults with generalized anxiety disorder, social anxiety disorder, panic disorder, and healthy controls at the MGH Center for Anxiety and Traumatic Stress Disorders assayed for PACAP by ELISA and radioimmunoassay.

**Results:** In our first set of samples (n=47) we found that PACAP in serum from males is often below the level of detection for the validated PACAP ELISA. Of the female samples (n=19), n=3 were healthy controls with PACAP below the level of detection, indicating a trend that elevated circulating PACAP may behave as a biomarker for those with anxiety-spectrum diseases. Of the 16 samples, diagnoses include GAD (n=5), SAD (n=4), and panic (n=4). PACAP serum levels were similar to those with PTSD (n=3), which we ran as a positive control. Data from RIA are forthcoming.

**Conclusions:** Circulating PACAP is elevated in females with a diagnosis of any anxiety-related disorder. We plan to analyze this and additional serum PACAP data with patient symptom questionnaires and sex hormone levels to ascertain the PACAP’s correlation with symptom profiles and estrous cycle state.

**Supported By:** Highland Family Foundation

**Keywords:** Biomarkers, Anxiety Disorder, Neuroendocrine, Gender differences
976. Estradiol, Cortico-Amygdalar Structural Networks and Cognitive Development

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**Background:** Estradiol is thought to be centrally involved in CNS masculinization, particularly in limbic regions such as the amygdala. It carries both neuroprotective and neurotoxic actions in the developing brain, depending on cell type, brain region, and developmental period. Yet little is known about estradiol-related structural brain phenotypes during adolescence and its association with sex-specific cognitive development in humans.

**Methods:** We used data from the NIH Study of Normal Brain Development (n = 433 children with typical developmental trajectories, followed longitudinally every 2 years with structural MRIs, hormonal and pubertal measurements, and neurocognitive testing). Mixed effects models were used to test the relationship between estradiol, cortico-amygdalar structural covariance and tests of reading skills (typically better in females) as well as spatial working memory (typically better in males) in a sub-sample of boys and girls (pre-menarche) matched for pubertal stage.

**Results:** Estradiol levels were associated with structural covariance between the amygdala and the posterior cingulate cortex, the frontal eye fields, and the retrosplenial cortex, but only in younger children. This effect decreased over time, such that it became non-significant in older adolescents. Estradiol’s influence on cortico-amygdalar structural networks was also associated with lower reading skills and higher spatial working memory.

**Conclusions:** Estradiol may impact the development of functionally relevant cortico-amygdalar structural networks, but this effect decreases steadily across adolescence. Estradiol’s influence on structural networks may improve performance on tests measuring ‘male-typical’ cognitive skills, and impair performance on tests measuring ‘female-typical’ skills, supporting previous evidence of estradiol’s role in masculinization of the brain.

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977. The Attenuation of Attunement: Poverty Negatively Impacts the Coordination of Mother-Child Adrenocortical Activity

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**Background:** The attunement of physiological activity between individuals has been suggested to shape early-life development and may be particularly important in contexts of adversity. Child and caregiver adrenocortical attunement may influence the development of stress regulation and impact social-emotional and behavioral outcomes. To better understand adrenocortical attunement, we examined the relation between poverty and cortisol (CORT) activity in mother-child dyads.

**Methods:** Participants were drawn from a large, longitudinal sample (N = 1,292) of families living in rural poverty. Children participated in a mask presentation stressor task at ages 7, 15, and 24 months. CORT was assayed from mother’s and child’s saliva collected at baseline, immediately prior to the stressor, and 20 and 40 minutes post stressor. Using a mixed linear regression model, we predicted within-person change in child CORT from the average of mother’s CORT and poverty-related risk at each time point.

**Results:** Mother’s CORT predicted child’s CORT at 7 (β = -0.105, p = 0.017) and 15 months (β = -0.133, p = 0.006). Mother’s CORT also significantly interacted with poverty-related risk at 15 (β = -0.137, p = 0.045) and 24 months (β = -0.130, p = 0.041). These effects were predictive over and above numerous relevant covariates including time of day of saliva collection.

**Conclusions:** These findings reveal that mother-child CORT attunement was significantly attenuated by poverty-related risk, such that dyads with higher risk displayed lower levels of attunement. Additionally, these negative effects of poverty appeared to emerge over the first two years of life. Overall, this study draws attention to the early-life impacts of socioeconomic factors on mother-child physiological attunement.

**Supported By:** DGE1342536, National Science Foundation; 1PO1HD39667 & 2PO1HD039667, National Institute of Child Health and Human Development

**Keywords:** cortisol, attunement, socioeconomic status, parenting, development

978. Methodological Approaches to the Study of Neuroendocrine and Inflammatory Biomarkers of Childhood Trauma: A Systematic Review

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**Keywords:** Estrogen, Puberty, Human Brain, Neuroimaging, Adolescence
**Background:** Childhood trauma (CT) has been robustly linked to physical and mental illness, with the hypothalamic-pituitary-adrenal (HPA)-axis and inflammatory systems implicated as putative mechanisms underlying this relationship. Further, the HPA-axis and inflammatory systems act synergistically. However, methods examining the relationship between CT and biological disruption vary widely.

**Methods:** A systematic review was conducted using key search terms (e.g., childhood trauma, cytokines, HPA-axis) through PubMed, yielding 345 original empirical articles meeting criteria. All studies were coded for the following themes: age of population, CT measure, and assessment of HPA-axis functioning and inflammation.

**Results:** Over half of the studies measured CT via retrospective self-report measure, the Childhood Trauma Questionnaire (CTQ), and over 62% of studies were conducted in adult/geriatric samples. Several measures of HPA-axis functioning were utilized: salivary cortisol (50%) was the most used. For cortisol analysis, stress test/reactivity was the most common analytic approach (32%) followed by diurnal slope (28%). While over 30 inflammatory biomarkers were tested across studies, C-reactive protein (CRP) and interleukin-6 (IL-6) were the most reported inflammatory biomarkers measuring immune functioning. Elevated levels of CRP and IL-6 were the most consistently correlated with CT, though results varied across studies. Notably, only 4% of studies investigated both HPA-axis and inflammation.

**Conclusions:** Few studies examine pediatric populations and most studies in the field are limited by retrospective self-report of CT. Further, only a small portion of studies examined neuroendocrine and inflammatory functioning in concert. Future studies with developmental populations and multi-methodological approaches need to be conducted to address these gaps.

**Keywords:** HPA axis, Inflammation, Childhood Trauma, Cortisol, Cytokine

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**979. Among Pregnant Women Early Life Stress (ELS) is Associated with Heightened Inflammatory Response to Acute Stress**

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**Background:** Preliminary data from our P50-funded research suggest that maternal experiences of early life stress (ELS), before conception of offspring, may affect timing of delivery and neonatal outcomes. Spontaneous preterm birth (SPTB) has been associated with both ELS and inflammation, suggesting potential links. Indeed, ELS heightens inflammatory response to acute stress in adulthood, but this has not been assessed during pregnancy. This study aims to assess proinflammatory cytokine response to acute stress in high versus low ELS pregnant women.

**Methods:** Healthy female participants were recruited at 21-32 weeks gestation. Structured Clinical Interview for DSM (SCID) confirmed healthy psychiatric status and Edinburgh Postnatal Depression Scale (EPDS) assessed depressive symptoms. Women completed the Adverse Childhood Experiences (ACE) Scale to assess ELS and underwent a laboratory stressor (Trier Social Stress Test; TSST) from T=0 to T+20 minutes. Serum interleukin-6 (IL-6) was collected at T-5, T+5, T+30, T+65, T+140. ACE was categorized as low (0-1) or high (>=2). Repeated measures ANOVA assessed effects of ACE group and time.

**Results:** High ACE women had significantly elevated IL-6 compared with low ACE women across the four TSST timepoints in a significant ACE x time interaction (p=0.047). Women were similar across ACE groups in demographics and EPDS score (p’s > 0.05).

**Conclusions:** Women with a history of ELS had heightened inflammatory response to acute stress in this ongoing study, a novel finding in pregnant women. As inflammation has been associated with preterm birth, exaggerated inflammatory response to stress during pregnancy may play a role in SPTB.

**Supported By:** March of Dimes Prematurity Research Center at the University of Pennsylvania

**Keywords:** perinatal, transgenerational, Early Life Stress, preterm, Interleukin-6

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**980. Insulin is a State Biomarker in Major Depressive Disorder: A Systematic Review and Meta-Analysis**

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**Background:** Alterations in energy metabolism have been latterly implicated in the physiopathology of major depressive disorder (MDD). Insulin resistance and hyperinsulinemia are features commonly described in major depression, however, data regarding this topic is still conflicting, as is the effect of antidepressants. The aims of this study were to verify if peripheral insulin levels are altered in MDD.

**Methods:** This study is comprised of a meta-analysis comparing insulin levels in an acute MDD episode in drug-free persons, in an acute MDD episode in medicated persons, and in remitted MDD in medicated persons, to its levels in healthy controls. Results from different studies were pooled using random effects.

**Results:** Thirty-eight studies were included, providing data on 31,763 participants. Insulin levels were moderately increased in subjects in a current major depressive episode when compared to healthy controls, both in those without antidepressants (g=0.45, 95% CI 0.08 to 0.83, p=0.018) and in those on antidepressants (g=0.38, 95% CI 0.17 to 0.59, p<0.001). There were no differences in insulin levels in persons with major depression during remission when compared to healthy controls (g=0.11, 95% CI -0.13 to 0.36, p=0.351).
Conclusions: Our study provides evidence that insulin levels are increased in acute episodes of MDD regardless of antidepressant medication status, and that these alterations are not found in remission. This supports the notion that energy metabolism is altered in MDD, and that this alteration is dynamic in nature, with insulin being a possible biomarker of state and disease activity in MDD.

Keywords: Precision Medicine, Biomarkers, translatable biomarker, Mood disorders

981. Hypothalamic Pituitary-Adrenal Axis Homeostasis in Response to Chronic Foraging Uncertainty in Vulnerable Macaque Mothers: Contrasting Individual versus Social Allostasis

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Background: Despite group activation of the maternal corticotropin-releasing factor (CRF) system in response to an “allostatic load” – a model of food uncertainty termed maternal variable foraging demand (VFD) – group activation of the maternal hypothalamic-pituitary-adrenal (HPA) axis was notably absent. Individual chronic homeostatic stress adaptations of the HPA axis may offer a second order of homeostasis, a process we provisionally term “social allostasis”.

Methods: Twenty-two socially housed bonnet macaque maternal-infant dyads were exposed to VFD of alternating two-week epochs of low or high foraging demand disrupting the maternal repertoire in normative infant rearing. Cerebrospinal fluid (CSF) CRF concentrations and plasma cortisol were measured pre- and post-VFD (Δ=post−pre-VFD). Dyadic distance was measured and pre-VFD social ranking assessments were performed by blinded observers.

Results: Despite marked individual cortisol responses (mean of individual Δ /pre-VFD=19.8 %) there was an absence of maternal HPA axis group mean response to VFD (0.0 %). By contrast, although individual CSF CRF increases in concentration (mean of individual Δ /pre-VFD=56 %) were observed, group mean exhibited activation by almost 25% (p=.002). A “dyadic vulnerability” index (low infant weight, low maternal weight, subordinate maternal social status and reduced dyadic distance) predicted maternal cortisol decreases (p<.0001).

Conclusions: In response to a chronic stressor, dyadic vulnerability plays a significant role in determining the directionality and magnitude of individual maternal HPA axis responses in the service of maintaining a “social” version of HPA axis homeostasis, provisionally termed social allostasis.

Supported By: RO1 MH

Keywords: Social Allostasis, HPA axis, Variable Foraging Demand, CRF, Dyadic Vulnerability

982. Biosignatures of Suicidal Subtypes: Fleeting Suicidal Ideation and Low Suicide Intent Are Associated with Stress Response

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Background: Suicidal behavior (SB) is heterogeneous, and thus defining more homogeneous subgroups may improve the prediction and treatment of suicide. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been noted in individuals with SB and may identify a specific suicidal phenotype. We hypothesized that those with fleeting suicidal ideation (SI) and suicidal intent would show greater stress-responsivity.

Methods: Fifty-seven individuals with major depressive disorder (MDD); 19 suicide attempters and 38 non-attempters, aged 18-65 years participated in the Trier Social Stress Test (TSST), a well-established social stress experimental procedure. Salivary cortisol was measured at 5 time-points during the TSST and response was defined as area under the curve (AUC). SI was assessed by Beck Scale for Suicidal Ideation (SSI). Correlations of baseline cortisol and AUC with the total SSI and duration of SI for all participants, and with the Suicide Intent Scale for attempters was obtained.

Results: The total SSI score was not associated with cortisol response AUC. However, subjects who reported brief, fleeting ideation had significantly higher cortisol response than others (b= 18.14, t= 2.86, p<.05). Within the attempter group, higher suicidal intent was negatively related to cortisol response (Pearson’s r= −0.51, p= <0.05). Baseline cortisol was neither related to SI nor to suicide intent.

Conclusions: These findings support the existence of a stress-responsive subtype of suicidal individuals. Consistent with previous studies, hyper-responsiveness of HPA axis to stress might be associated with brief, fleeting SI as well as with low intention for completing suicide. This might have future implications in suicide prevention and treatment.

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Keywords: Trier Social Stress Test, Suicidal ideation, Cortisol, Depression, suicidal intent
983. Dysregulated Diurnal Cortisol Pattern and Heightened Afternoon Cortisol in Individuals with Bipolar Disorder

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**Background:** Evidence supports dysregulated cortisol patterns in bipolar disorder (BD). However, whether this dysregulation occurs throughout the day or at a specific time is unclear. The objective of this study was to specifically determine when during the day, individuals with BD demonstrate abnormal cortisol levels compared to healthy controls (HCs).

**Methods:** Twenty-seven individuals with current BD I or II and thirty-one HCs were recruited. Salivary cortisol was measured at six time points (at wake, 15 minutes after wake, 30 minutes after wake, 45 minutes after wake, from 2-4 pm, and at 10 pm) for three consecutive days. Analysis was conducted to determine at what times of day participants with BD had significantly higher cortisol than HCs.

**Results:** Adjusting for body mass index (BMI) and smoking status, the mixed-effects model showed a significant interaction effect between group and time of day (p = 0.02), and a main effect of BD vs HCs (p < 0.001). BD participants in a currently mixed episode state showed significantly higher cortisol levels than the HCs at all time points except for 10 pm (p < 0.05); currently depressed episode BD participants had significantly higher cortisol levels than HCs 45 minutes after waking and at the 2-4 pm time point (p < 0.05).

**Conclusions:** We found that the BD group had significantly higher cortisol levels than HCs. The more pronounced awakening response seen in BD, particularly in the mixed episode group, suggests a hyperactivity of the HPA axis that could relate to dysregulation in mood.

**Supported By:** NIH KL2

**Keywords:** Cortisol, Bipolar Disorder, Mood disorders, neuroendocrinology

984. HPA Axis Functioning in Depressed Adolescents with and without Non-Suicidal Self-Injury

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**Background:** Non-suicidal self-injury (NSSI) is characterized by causing harm to one’s own body without the intent of suicide, and is hypothesized to be a coping mechanism for acute stressors. Some preliminary research has indicated that those with NSSI show blunted HPA reactivity in response to an acute stressor, demonstrating an allostatic shift in functioning. However, further replication is needed.

**Methods:** The present study examines salivary cortisol release following the Trier Social Stress Test (TSST) in adolescents (N = 153) with major depressive disorder (MDD) and NSSI adolescents with MDD and no NSSI, and healthy controls. The presence of MDD and/or NSSI was determined using the KSADS-PL (Kaufman et al., 1997). We examined salivary cortisol levels at five time points following the TSST, while controlling for gender.

**Results:** Our results suggest reduced cortisol release and heightened stress in individuals who self-harm. At four of the five time points, we discovered trending significance between the three groups. At t3 (45 minutes post-TSST), we observed that those with MDD and NSSI had significantly lower cortisol levels than those with MDD and no NSSI (p = .004). Self-reported stress levels for those with MDD and NSSI were also significantly higher than controls following the social stressor (p < .001).

**Conclusions:** These findings advance previous physiological research on NSSI. The trending significance found in the present study is consistent with the theory of hypo-responsiveness in NSSI (Kaess et al., 2011). Future, longitudinal research should be conducted to determine the temporal relationship between NSSI and a disrupted HPA axis.

**Supported By:** NIMH K23MH090421, Minnesota Medical Foundation, National Alliance for Research on Schizophrenia and Depression

**Keywords:** Major Depressive Disorder (MDD), Non-suicidal self-injury, HPA axis, Cortisol, Trier Social Stress Test

985. Association between Depressive Symptom Profiles and Stress Reactivity in Adolescents

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**Background:** Altered hypothalamic-pituitary-adrenal (HPA) function is common in adolescents with major depressive disorder (MDD) but variability in the strength and direction of HPA alterations has prompted a search for symptom-based subtypes with unique neuroendocrine signatures. This study investigated the extent to which depressive symptom profiles were differentially associated with cortisol responses to psychosocial stress.

**Methods:** A total of 145 adolescents who varied in their risk for MDD were recruited: 38 met criteria for current MDD; 35 had no personal history of a psychiatric disorder but were at high risk for MDD based on having one or both parents with unipolar MDD; and 72 had no personal or family history of a psychiatric disorder (low-risk youth). Following semi-structured diagnostic assessments and rating scales, salivary cortisol responses to the Trier Social Stress Test (TSST) were measured. Multilevel models examined within-person change in cortisol levels during the 2-hour resting phase prior to the TSST and both linear and
conclusions: These findings suggest that heterogeneity among studies examining HPA reactivity in depressed youth may be driven, in part, by differences in depressive symptom profiles across samples.

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Keywords: major depressive disorder; depressive symptoms; adolescence; stress; TSST

986. Inflammatory Cytokines in a Repeated Measures Prospective Case Study of Interferon-Induced Depression

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Background: Cytokines have been implicated in the genesis of depression. Inflammatory changes and their relation to melatonin were examined during the course of interferon-induced depressive symptoms.

Methods: A patient with hepatitis C virus infection was monitored during treatment with interferon-α from baseline, after one, two, three and six months of treatment to three months past treatment. Repeated psychiatric assessments included the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version and self-rating scales Montgomery Asberg Depression Rating Scale (MADRS-S). Markers previously related to cytokine-induced depression were analyzed in plasma using multiplex proximity extension multiplex assay (PEA). Melatonin in saliva was analyzed with competitive ELISA.

Results: This patient developed a DSM IV major depressive episode and MADRS-S score was 2 at baseline, 23, 26, 21, 31 during treatment and 2 post-treatment. She was treated with Venlafaxine. IL-7 was negatively correlated to MADRS-S (r = -0.812 p = 0.050), IL-18 was correlated to MADRS-S (r = 0.986 p < 0.000), IL-6 and IL-10 were not significantly correlated to MADRS-S (both r = 0.754 p = 0.084). While MADRS-S was not significantly correlated to bedtime melatonin (r = -0.794 p = 0.059), IL-10 and IL-18 were correlated to bedtime melatonin (both r = -0.841 p = 0.036). BDNF was not correlated to MADRS-S (r = -0.493 p = 0.321), however, BDNF correlated to morning levels of melatonin (r = 0.812 p = 0.050).

Conclusions: This prospective case study with repeated measures corroborates previous findings that IL-6, IL-7, IL-8, IL-10, and IL-18 change during depression. Both morning and evening levels of melatonin were reduced and the results support cytokine involvement. PEA may be a useful method to identify novel markers for depression.

Supported By: ALF-funds Uppsala University Hospital

Keywords: Interferon-induced depression, Depression, Melatonin, Cytokines and Chemokines, Hepatitis C

987. Stress Reactivity, Cortisol Levels and Experience Sampling in Adults with 22q11DS

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Background: 22q11 deletion syndrome (22q11DS) is a genetic disorder associated with anxiety and mood disorders, and increased risk for psychosis. Cortisol levels and stress reactivity reflect hypothalamic-pituitary-adrenal (HPA)-axis activity and are believed to be altered in subjects that often experience daily life stress, mood- and psychotic symptoms. However it is unknown whether patients with 22q11DS have an altered stress reactivity.

Methods: We included 27 adults with 22q11DS (age: 34.4 years, 66.7% female) and 24 healthy controls (HC) (age: 36.5 years, 68.6% female). The experience sampling method (ESM) was used and at every assessment a saliva cortisol sample was taken. Cortisol samples were averaged and compared between groups using an independent t-test and a multilevel regression model was used to analyze the ESM data.

Results: Cortisol was significantly lower in the 22q11DS group (t(57) = 11.1, p < .001) compared to healthy controls. In addition event-related-stress reactivity scores were a negative predictor for average self-reported negative affect in both 22q11DS patients and healthy controls, respectively $R^2 = 0.130$, $F(2,1155) = 87.82$, $p < .001$ and $R^2 = 0.0578$, $F(2,1120) = 35.4$, $p < .001$ and significantly higher in 22q11DS compared to healthy controls ($z = -2.430$, $p < .05$).

Conclusions: These preliminary results indicate that people with 22q11DS may experience higher self-reported negative affect to small stressors in daily life, whilst showing lower mean cortisol levels than HC, possibly resulting from an over sensitization of the HPA-axis, which gives rise to hypocortisolism in posttraumatic stress disorder and psychotic major depression. This could imply a permanent long-term effect of stress and possibly be present in adults with 22q11DS too.

Keywords: 22q11 Deletion Syndrome, Cortisol, ESM, Stress Reactivity
988. Gender Difference in Association of Obesity with Serum BDNF in Chinese Patient with Chronic Schizophrenia
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Background: Brain-derived neurotropic factor (BDNF) plays fundamental role in the regulation of neuronal survival, differentiation and synaptic plasticity in the peripheral and central nervous systems. BDNF levels were reduced in drug-naive, first-episode schizophrenia and increased with antipsychotic treatment. In addition, circulating BDNF levels were lower in individuals with obesity than those without obesity and weight reduction program significantly increased BDNF levels. However, very few studies have explored gender differences in the relationship of serum BDNF levels and obesity in chronic schizophrenia patients.

Methods: Using sandwich ELISA, we compared the serum BDNF levels in 20 obese chronic schizophrenic patients (male/female=9/11) and 113 non-obese patients (male/female=89/24). Regression studies were used to assess the association of BMI with BDNF levels in both genders.

Results: There was a significant difference in serum BDNF levels between male and female patients (6.99±5.44 vs 5.82±4.08 respectively, p=0.006). Obese female patients has a significant lower BDNF levels compared to non-obese female patients (4.92±1.32 vs 6.20±2.16, p=0.04), while there was no significant difference between obese and non-obese in male patients. In female, the serum BDNF levels was inversely associated with changes of BMI (r=-0.61, p=-0.21, p=0.04), while there is no association between BDNF levels and BMI in male patients.

Conclusions: Out results indicate significant gender differences in the association of peripheral BDNF levels with BMI. BDNF levels were inversely associated with BMI in female chronic schizophrenic patients while there was no such association in male patients.

Keywords: Schizophrenia, BDNF, Obesity

989. Neural Responses to Emotional Stimuli in Individuals with PTSD after Daily Morning Blue Light Exposure
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Background: Two of the most prevalent symptoms in post-traumatic stress disorder (PTSD) are emotion regulation difficulties as well as sleep problems. Morning blue light exposure (BLE) has been used as a way to improve sleep, and acute BLE has been shown to modulate brain activation changes during anticipation of emotional stimuli in healthy individuals. This study assessed whether six weeks of daily morning BLE can reduce PTSD symptom severity and lead to changes in individuals' functional brain responses when anticipating aversive emotional stimuli.

Methods: Fourteen individuals (50% female) with a clinical diagnosis of PTSD were randomly assigned to receive either six weeks of 30 minutes of morning BLE (active condition, n=9) or amber light (placebo condition, n=5). Before and after the intervention, participants completed the Clinician Administered PTSD Scale for DSM-5 (CAPS-5) and underwent fMRI while completing an emotional anticipation task.

Results: While there was no difference in CAPS-5 symptom scores from pre- to post-light exposure between the two groups (F(1,12)=.09, p=.78), participants in the BLE group showed an increase in activation within the right medial frontal gyrus and a decrease in activation within the right insula when anticipating negative versus positive stimuli (p=0.005, uncorrected).

Conclusions: The results suggest that daily BLE may alter responses in brain regions linked to emotion regulation. As we found no differences in PTSD symptoms between the two groups, it is unclear whether these neuronal changes correspond to changes in cognitive or behavioral emotion regulation abilities. Future research with larger sample sizes should therefore examine this intriguing possibility.

Supported By: UASMRAA
Keywords: BOLD fMRI, blue light, PTSD

990. Effects of Post-Exposure Naps and Home Sleep on Exposure Therapy for Social Anxiety
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Background: In persons with social anxiety, we investigated whether naps following social exposure sessions might enhance consolidation of therapeutic extinction memory and thereby improve clinical outcomes.

Methods: Thirty-two participants aged 18-39 (18 females) with mean Liebowitz Social Anxiety Scale (LSAS) scores of 84.5 (91%) ≥60 completed 5-week exposure-based, group therapy for social anxiety. Before and after treatment, participants underwent a modified Trier Social Stress Test (mpTSST) with skin conductance level (SCL), electromyography and electrocardiography. An auditory startle procedure occurred while participants were preparing their speech. Therapy sessions 3&4 had exposures followed by either a 120-min nap opportunity (N=17) or non-arousing video (N=15). Sleep throughout the 7-week study was monitored with actigraphy and diaries. High-and low-responders were defined by median splits of percentage improvement on LSAS total, fear and avoidance scores and Social Anxiety in Adults (SAQA) scores.

Results: Sympathetic activation during mpTSST decreased more across treatment in the Nap arm. Arm (nap, wake) x Test
(pre-, post-treatment) interaction trends were seen for startle SCR [F(1,28)= 2.81, p = .105], SCL during speech [F(1,23)= 4.54, p = .04], and post-mpTSST cortisol [F(1,26)= 2.93, p = .099] all reflecting significant decrease in Nap (p < .05) but not Wake arms. No differences appeared in self-report indices or other mpTSST measures. High responders for LSAS-fear had greater diary-based SE and shorter SOL (mpTSST) measures. High responders had greater morningness (p < .05) measured objectively (actigraph sleep midpoint) or subjectively (diary and questionnaire).

Conclusions: In exposure treatment for social anxiety, post-exposure naps lowered sympathetic responses to a social challenge but not clinical indices. Patients with better clinical outcomes showed better habitual sleep quality and greater morningness.

Supported By: NIH/NIMH R21MH103484

Keywords: anxiety, sleep, exposure therapy, extinction, psychophysiology

991. Oscillation Changes in EEG Measured in the On and Off DBS State in Patients with Treatment Resistant Depression

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Background: Trials using deep brain stimulation (DBS) of subgenual cingulate (SCG) have shown promise as an effective therapy for some patients with treatment resistant depression (TRD), although reliable biomarkers of response have yet to be found. Two studies of resting EEG showed that hemispheric asymmetry and frontal theta cordance distinguish SCG-DBS responders and non-responders. However, none have investigated how EEG differences between DBS ON and OFF states relates to treatment response.

Methods: Eight TRD patients receiving SCG-DBS had EEG and symptom severity (Hamilton Rating Scale for Depression (HDRS)) collected at baseline, 1 and 3 months post-surgery. EEG resting-state recordings were taken in the DBS ON and OFF (20 mins) states with EEG power and asymmetry scores calculated for each.

Results: The difference between ON and OFF states in frontal alpha (r = 0.738, p = 0.037) and beta (r = 0.881, p = 0.004) asymmetry predicted early (1 month) HDRS change. Comparing spectral content in ON and OFF states revealed a global increase in delta and decrease in theta/alpha/gamma. Delta differences between ON and OFF states negatively correlated with theta/alpha/beta power. These differences were also predictive of early (3 months) treatment response (r = 0.795/0.868/0.759, p = 0.018/0.005/0.029).

Conclusions: In this preliminary analysis in a limited number of patients, the effect of SCG-DBS on frontal asymmetry predicted early changes in depressive symptoms. Broadband shifts from the DBS ON to OFF state also suggest cross-frequency coupling between delta and alpha/beta band activity relating to response. These differences in oscillatory coupling could index changes in neural communication relating to the underlying mechanism of SCG-DBS.

Supported By: Alberta Innovates Health Services (AIHS), Collaborative Research Innovation Opportunity

Keywords: Treatment Resistant Depression, Deep Brain Stimulation, EEG

992. Cortical Thickness and Response to Repetitive Transcranial Magnetic Stimulation in Youth with Major Depressive Disorder

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Background: Current treatment options for major depressive disorder (MDD) in youth are limited. Repetitive transcranial magnetic stimulation (rTMS) is an emerging intervention for treatment resistant major depressive disorder (MDD) in youth. We hypothesize that the target site for rTMS, the dorsolateral prefrontal cortex (DLPFC), will differ in cortical thickness between responders and non-responders to treatment.

Methods: Anatomical data was collected on a 3.0T GE MR750w. A 15-weekday rTMS treatment was applied targeting the left DLPFC (120% RMT, 75 Trains/3000 pulses per session) in 22 youth with treatment resistant MDD (13 – 21 years). FreeSurfer was used for cortical reconstruction.

Results: No significant adverse events were reported. Half of participants (n=11) responded to rTMS treatment with a greater than 50% reduction in Hamilton Depression Rating Score (range -17.65 to 78.95%, mean 45.21%, SD ± 25.43). At baseline, responders had thinner left rostral middle frontal (p=0.0001) and right superior frontal (p=0.006) regions compared to non-responders. Change in Hamilton depression rating score negatively correlated with right lateral orbitofrontal cortical thickness in responders (p=0.003).

Conclusions: rTMS is an effective treatment method for youth with treatment resistant MDD. Our data demonstrates a relationship between decreased regional cortical thickness and response to rTMS in youth with MDD. Identification of a morphological biomarker of response in adolescent major depression has considerable clinical implications and lends insight to the pathophysiology of depression.

Supported By: Alberta Children’s Hospital Research Institute (ACHRI); Children's Hospital Aid Society (CHAS)

Keywords: Cortical Thickness, Transcranial Magnetic Stimulation, Biomarkers, Major Depressive Disorder (MDD), Adolescents

993. Increase in Theta Cordance May Predict Early Antidepressant Response to ECT in Older Adults

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Background: Theta oscillations are generated by various brain structures associated with depression, including medial prefrontal
(mPFC) and anterior cingulate cortex (ACC). Theta cordance (TC) is a related measure believed to reflect local energy consumption in these regions and is predictive of treatment response in depression patients. Although pharmacological studies have shown decreased TC after successful intervention, a recent study of TC among responders to deep-brain stimulation (DBS) for depression demonstrated increased TC. One potential explanation for this differential effect is intervention type (pharmacological vs. electrical stimulation).

**Methods:** We used magnetoencephalography (MEG) to localize cortical TC changes in eight patients (mean 63 yo) with treatment-resistant depression before and after seven sessions of electroconvulsive therapy (ECT). Response was defined as ≥30% improvement on the Hamilton Depression Rating Scale (HDRS).

**Results:** Five patients responded to treatment (48% average HDRS decrease). We noted a significant increase in TC in responders relative to non-responders in a right mPFC cluster (permutation test, p=0.03; average TC change: +0.90 [135% increase] for responders, −0.64 [98% decrease] for nonresponders). Responders additionally showed diffuse frontal increases and occipito-parietal decreases in TC.

**Conclusions:** Our study is the first to use MEG to localize TC activity to the mPFC. Our results are in accordance with a recent DBS study of TC which also showed increased frontal TC among responders, and mPFC changes shown using PET during successful depression treatment. Our findings suggest a treatment class effect, in which frontal TC increases with successful stimulation treatments and decreases with successful pharmacological treatments.

**Supported By:** CIHR

**Keywords:** Depression, geriatric, Electroconvulsive therapy (ECT), Magnetoencephalography, Biomarkers

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**994. A Randomized Comparison of 1 Hz Vs. 20 Hz Vs. Sham Dorsomedial Prefrontal rTMS for Treatment-Resistant Depression: Preliminary Clinical Results**

**Katharine Dunlop**<sup>1</sup>, Jack Sheen<sup>2</sup>, D Blake Woodside<sup>3</sup>, Patricia Colton<sup>2</sup>, Marion Olmsted<sup>2</sup>, Kfir Feffer<sup>2</sup>, Daniel M. Blumberger<sup>4</sup>, Zafiris Daskalakis<sup>5</sup>, Peter Giacobbe<sup>1</sup>, and Jonathan Downar<sup>6</sup>

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**Background:** Bilateral dorsomedial prefrontal cortex (DMPFC) rTMS has previously been used in open-label settings for treatment resistant depression (TRD). However, its clinical efficacy is heterogeneous, and requires testing under placebo-controlled conditions. The aim of this study is to assess the efficacy of two protocols for DMPFC-rTMS in TRD against sham stimulation. Here we report preliminary results of the first 30 subjects enrolled.

**Methods:** rTMS-naïve TRD patients between 18-65 years were enrolled and randomized to one of three treatment arms: 1Hz active, 20Hz active, or sham rTMS to the bilateral DMPFC. All treatments were performed with a custom active-placebo coil to allow blinding of patients and technicians. Treatments occurred twice daily for a total of 30 sessions. A repeated-measures ANOVA on primary clinical measures was performed to determine the effects of treatment group on severity.

**Results:** To date, 30 participants (n=20 females, range 19-58 years) have completed treatment. We found a trend in the interaction between BDI severity and treatment arm, and a significant main effect of time on BDI. Both Group A and Group B improved significantly. Group C, however, had a nonsignificant reduction on BDI.

**Conclusions:** Although preliminary, it appears that two treatment arms (treatment arms A and B) achieve a significant reduction of depressive symptoms relative to treatment arm C. Further work will enrol more patients in this study to confirm the effects of DMPFC-rTMS in TRD. We are also collecting a battery of psychometric, behavioural and neuroimaging measures to identify predictors of and measures that change in association with treatment response.

**Supported By:** CIHR

**Keywords:** Treatment Resistant Depression, rTMS, Dorsomedial Prefrontal Cortex

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**995. Neural Correlates of Successful Inhibitory OFC-rTMS in Major Depressive Disorder**

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**Background:** rTMS, a safe and effective option for major depressive disorder (MDD), typically targets the dorsolateral prefrontal cortex (DLPFC), or occasionally the dorsomedial prefrontal cortex (DMPFC); however, many patients do not respond to rTMS of these regions. As is becoming increasingly clear that the orbitofrontal cortex (OFC) plays a critical role in the pathophysiology of MDD, inhibitory OFC-rTMS may be potentially therapeutic for those patients who do not respond to standard rTMS treatments.

**Methods:** 10 MDD patients underwent 30 sessions of inhibitory (C-TBS) right OFC-rTMS. Resting-state (rs) fMRI scans were collected before and after treatment (n=8). Remission was defined as a score of ≤7 on the clinician-administered Hamilton Rating Scale for Depression (HRSD17). For pre- and post-treatment rs-fMRI, cortico-subcortical connectivity predictors and correlates of response were examined with seed-based correlation analyses (using the bilateral nucleus accumbens [NAcc] as a priori regions of interest).

**Results:** 4 out of 10 patients achieved response (>50% symptom reduction), with 3/10 reaching remission. HRSD scores overall improved by 33%+/−SD35%. Low baseline connectivity between the NAcc and bilateral fusiform gyri
predicted percent improvement, while increased connectivity between the NAcc and the ventromedial prefrontal cortex (VMPFC) correlated to percent improvement.

**Conclusions:** This is the first report demonstrating efficacy of OFC-rTMS as a treatment for depression specifically. Neuroimaging suggests that OFC-rTMS may achieve therapeutic effect by a distinct mechanism from conventional DL- or DMPFC-rTMS, via increases in NAcc-VMPFC connectivity. fMRI biomarkers could potentially allow personalization of rTMS treatment parameters.

**Supported By:** CIHR; Toronto Western Hospital Foundation

**Keywords:** rTMS, Depression, Orbitofrontal Cortex, fMRI, Biomarkers

996. The Effect of Exercise Training on Resting Concentrations of Peripheral Brain-derived Neurotrophic Factor (BDNF): A Meta-analysis

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**Background:** The mechanisms through which physical activity supports healthy brain function remain to be elucidated. One hypothesis suggests that increased brain-derived neurotrophic factor (BDNF) mediates some cognitive and mood benefits. This meta-analysis sought to determine the effect of exercise training on resting concentrations of BDNF in peripheral blood.

**Methods:** MEDLINE, Embase, PsycINFO, SPORTDiscus, Rehabilitation & Sports Medicine Source, and CINAHL databases were searched for original, peer-reviewed reports of peripheral blood BDNF concentrations before and after exercise interventions ≥ 2 weeks. Risk of bias was assessed using standardized criteria. Standardized mean differences (SMDs) were generated from random effects models. Risk of publication bias was assessed using funnel plots and Egger’s test. Potential sources of heterogeneity were explored in subgroup analyses.

**Results:** In 29 studies that met inclusion criteria, resting concentrations of peripheral blood BDNF were higher after intervention (SMD = 0.39, 95% CI: 0.17 – 0.60, p < 0.001). Subgroup analyses suggested a significant effect in aerobic (SMD = 0.66, 95% CI: 0.33 – 0.99, p < 0.001) but not resistance training (SMD = 0.07, 95% CI: -0.15 – 0.30, p = 0.52) interventions. No significant difference in effect was observed between males and females, nor in serum vs plasma.

**Conclusions:** Aerobic but not resistance training interventions increased resting BDNF concentrations in peripheral blood.

**Keywords:** BDNF, exercise intervention, mood symptoms, cognition

997. Impact of Comorbid Psychological Trauma on Electroconvulsive Therapy Outcomes in Depression: A Retrospective Chart Review

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Centre for Addiction and Mental Health

**Background:** The influence of psychological trauma on electroconvulsive therapy (ECT) treatment outcomes in patients with depression is unknown. This goal of this study was to determine treatment response and ECT-related cognitive impairment (ECI) in clinical sample of patients with comorbid depression and psychological trauma.

**Methods:** We examined the clinical records of 72 patients, who received 95 acute courses of ECT, treated at an academic mental health hospital from October 2009 to September 2016. Included individuals had a DSM-V diagnosis of unipolar/bipolar depression and whose clinical records indicated a comorbid diagnosis of post-traumatic stress disorder (PTSD) or borderline personality disorder (BPD), which are both diagnoses associated with psychological trauma. Treatment response was determined by reviewing clinical notes to estimate clinical global impression improvement subscale and ECI was the global impression of cognitive impairment secondary to ECT as rated by the referring physician.

**Results:** The rate of treatment response was 67.4%. Factors associated with response were a lack of BPD diagnosis (60.9% responders vs 87.1% of non-responders), and greater number of ECT treatments (mean 11.3 vs 8.1). Factors not associated with response included age, depression type, psychosis, childhood trauma, electrode placement, or benzodiazepines. The rate of ECI was 25.8% and was associated with antiepileptic medication (2% without ECI vs 23.5% with ECI).

**Conclusions:** This work demonstrates ECT’s effectiveness for depression in individuals with psychological trauma histories. It highlights important clinical factors such as BPD diagnosis, number of treatments, and anti-epileptic medication as important clinical factors to consider when considering pursuing ECT in this patient population.

**Keywords:** Electroconvulsive therapy, PTSD - Posttraumatic Stress Disorder, Borderline Personality Disorder, Major Depressive Disorder (MDD), Trauma

998. The Combination of Mesenchymal Stem Cells and Lithium as an Immunomodulatory Strategy for the Treatment of Psychiatric Disorders

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**Background:** Immunological abnormalities have been implicated in the pathogenesis and physiopathology of psychiatric disorders. Accordingly, immunomodulatory approaches have
been proposed as a promising strategy for the treatment of major psychiatric disorders. In this scenario, mesenchymal stem cells (MSCs) have emerged as an important therapeutic tool due to their secretion of immunomodulatory and neurotrophic factors. We aimed to assess the immunomodulatory effects of co-cultivation of MSCs and neuronal cells challenged with D-amphetamine (D-AMPH).

**Methods:** SH-SYSY cells were differentiated into neuron-like cells using 10 μM retinoic acid for 7 days. On day seven, the co-cultivation with the MSCs was performed using a Transwell plate for 48h. In addition, treatment with lithium (1mM) was performed for 48h, alone or together with the MSCs. After 24h of those treatments, D-AMPH (2mM) was added to the cells, and the cells were then allowed to sit for another 24h. After the 48h treatment, the supernatant and cells were harvested, and intracellular and released levels of sIL-6RB, sIL-6Ra and sTNF-R1 were measured by multiplex.

**Results:** The co-treatment with MSCs and lithium decreased the intracellular levels of sIL-6RB, sIL-6Ra and sTNF-R1 in the cells treated with D-AMPH (p<0.05). The co-treatment with MSCs and lithium also decreased the secreted levels of sIL-6RB and sIL-6Ra from the cells stimulated with D-AMPH (p<0.05). Either MSCs or lithium alone was not capable to prevent the increase of these markers in neuronal cells stimulated with D-AMPH.

**Conclusions:** Our results suggest that MSCs and lithium have a synergic anti-inflammatory effect.

**Keywords:** Mesenchymal Stem Cells, Lithium, Immunomodulatory, Cytokines, D-amphetamine

### 999. Towards Targeted Training of Reinforcement Learning Alterations in Depression

**Vanessa Brown, Jacob Lee, Brooks King-Casas, and Pearl Chiu**

**Virginia Tech**

**Background:** A growing body of work links depression to altered reinforcement learning (Chen et al., 2015); some alterations predict and correlate with symptom improvement with standard treatments (Brown et al., 2016; Huys et al., 2016; Vrieze et al., 2013). Therefore, directly targeting reinforcement learning may lead to novel treatments. As an initial step towards developing a reinforcement learning retraining paradigm for treatment of depression, we tested the effectiveness of different strategies to alter learning parameters in a large, unselected sample.

**Methods:** Participants (n=617) were recruited via Amazon’s Mechanical Turk and randomly assigned to an experimental or control condition. Participants completed a probabilistic reinforcement learning task and, depending on the condition, were queried about different aspects of the task that, according to reinforcement learning theory and our preliminary neurobehavioral data in depression (Brown et al., 2016), were hypothesized to shift learning parameters. Participants’ choices were fit to a reinforcement learning model and tested for differences in parameters between the experimental and control conditions. Differences were also assessed in a subset of participants with clinically elevated depressive symptoms (n=172).

**Results:** Participants’ learning rates increased when asked about average stimulus values, while queries about comparing stimulus values increased perceived outcome value. Scaling of outcome value was not consistently affected by queries in participants with elevated depressive symptoms.

**Conclusions:** Specific aspects of learning implicated in the pathophysiology of depression can be modulated through targeted queries based on reinforcement learning theories. These data suggest the utility of this approach as a standalone intervention or when incorporated into existing treatments.

**Supported By:** R01MH106756

**Keywords:** Reinforcement learning, Depression, computerized tasks, Novel treatments

### 1000. High Frequency Repetitive Transcranial Magnetic Stimulation for Cognitive Impairment in Early-Phase Psychosis: A Pilot Study

**Michael Francis, Tom Hummer, Andrew Visco, Matthew Yung, Nikki Mehdiyoun, Teresa Kulig, Jenifer Vohs, Emily Liflick, and Alan Breier**

**Indiana University School of Medicine**

**Background:** Repetitive transcranial magnetic stimulation (rTMS) is a relatively new neuropsychiatric intervention. Approved for use in treatment resistant depression, investigators are now studying rTMS for other psychiatric diseases such schizophrenia. Cognitive dysfunction is a core facet of schizophrenia, present early in the course of the illness and contributing to diminished functioning and outcomes. In this study we examined the effect of high frequency rTMS on cognitive function in a group of individuals with early phase psychosis.

**Methods:** Twenty subjects were randomized (1:1), in double-blind fashion, to rTMS or sham condition. Over two weeks subjects underwent ten sessions of high frequency bilateral rTMS targeting the dorsolateral prefrontal cortex (DLPFC). Stimulation parameters were as follows: 110% of MT, 20 Hz, 30 trains, 1.0 second per train, 20 pulses per train, inter-train interval of 30 seconds (600 pulses/hemisphere, total of 1200 pulses/session/day). Prior to beginning and following completion of study treatment, subjects completed neurocognitive and symptom batteries and magnetic resonance imaging with resting state scan and in-scanner memory tasks.

**Results:** Subjects receiving active treatment demonstrated improved cognitive function as represented by the Brief Assessment of Cognition in Schizophrenia (BACS) total score (F = 4.633, p = .046). Additionally, there was a trend towards improved PANSS total score (F = 3.6, p = .074). There were no differences in working memory performance or activation. MRI data will be presented.

**Conclusions:** Preliminary results provide support for a potential therapeutic role of rTMS for cognitive impairment in schizophrenia. Additionally, rTMS was observed to be safe and well tolerated.

**Supported By:** NASSAD Young Investigator Award, Neuronetics Investigator Initiated Trial (IIT) program

**Keywords:** rTMS, cognition, recent-onset schizophrenia
1001. Neurocognitive Effects of Repeated Ketamine Infusions in Co-Occurring Posttraumatic Stress Disorder and Treatment-Resistant Depression

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**Background:** The glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine rapidly ameliorates posttraumatic stress disorder (PTSD) and depression symptoms in individuals with comorbid PTSD and treatment-resistant major depression (TRD). However, ketamine’s potential neurocognitive side effects have yet to be assessed in this population. The current study investigated 1) baseline neurocognitive performance as a predictor of ketamine treatment effect for PTSD and depression symptoms and 2) changes in neurocognitive performance after a ketamine repeated dosing regimen.

**Methods:** Adults with comorbid PTSD and TRD (n=16) received six intravenous infusions of 0.5 mg/kg ketamine over a 12-day period. Neurocognitive assessments occurred at baseline and within 7 days of infusion-series completion using components of theCogState battery. Primary outcome measures were collected immediately before and 24-hours after the final infusion and included the PTSD symptom Checklist (PCL-5) and the Montgomery-Asberg Depression Rating Scale (MADRS).

**Results:** Repeated ketamine infusions did not adversely effect cognition and cognitive measures were predictive of positive response to ketamine. Significant improvement was observed in scores of working memory (t=2.559, p=0.023) following completion of the infusion series compared to baseline. Greater improvement in PTSD symptoms was predicted by decreased working memory (F(1,11)=5.87, p=0.034) and slower set shifting (F(2,10)=8.353, p=0.007) at baseline. Lower attention at baseline was predictive of greater improvement in depression (F(1,12)=15.029, p=0.002).

**Conclusions:** This is the first study to examine the neurocognitive effects of repeated dosing of ketamine in a population of veterans with comorbid PTSD and TRD. Our findings suggest potential baseline neurocognitive predictors of ketamine response for separate PTSD and TRD symptom clusters.

**Supported By:** National Institute of Drug Abuse training grant (T32DA037183), Center for Epidemiological and Clinical Research (CECR)-VA Clinical Research Center of Excellence

**Keywords:** Ketamine, Post traumatic stress disorder, Treatment Resistant Depression, Neurocognition, PTSD depression

1002. Ketamine as a Treatment for Adolescent Major Depressive Disorder

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**Background:** Nearly 1 in 4 adolescents will experience major depressive disorder (MDD). Suicide is the 3rd leading cause of death in this age group. 40% of adolescents with MDD fail to respond to initial treatment with selective serotonin reuptake inhibitors (SSRIs). Of that SSRI-resistant population, nearly half remain depressed despite alternate medication and psychotherapy. Thus, better treatments for adolescent depression are urgently needed. Subanesthetic doses of ketamine, an NMDA antagonist, produce rapid antidepressant and anti-suicidal effects in depressed adults. There are few case reports and no prospective controlled trials of ketamine for the treatment of adolescent MDD.

**Methods:** We are conducting a midazolam-controlled crossover trial to evaluate the effects of ketamine in treatment-refractory adolescent MDD over four weeks. Adolescents must have failed at least one adequate trial of a standard antidepressant to enroll. Adolescents seeking ketamine treatment who do not meet inclusion criteria are referred to our Interventional Psychiatry Service on a case-by-case basis.

**Results:** We report a case of successful treatment of an adolescent with severe, medication-refractory MDD with suicidality who did not meet trial criteria, but was treated with ketamine through our interventional service. We demonstrate a rapid reduction of depressive symptoms (via CDRS and MADRS), suicidality (via SSI), and hopelessness (via BHS) that was sustained with a multiple infusion paradigm. Trial enrollment is ongoing.

**Conclusions:** Given the potential therapeutic benefits of ketamine and the burden of treatment-refractory adolescent MDD, ketamine deserves further study as a potential treatment in adolescents in appropriately supervised settings and with informed consent.

**Supported By:** Yale Child Study Center Pilot Award; AACAP Pilot Award

**Keywords:** Ketamine, Adolescent Depression, Suicide, Antidepressant, Glutamate

1003. Acute Ketamine Administration Corrects Abnormal Inflammatory Bone Markers in Major Depression

Bashkim Kadriu¹, Philip Gold¹, Marc Lener¹, Elizabeth Ballard¹, Mark Nicu², Peixiong Yuan³, David Luckenaugh¹, Rodrigo Machado-Vieira¹, and Carlos Zarate¹

¹National Institute of Mental Health, ²National Institutes of Health/National Institute of Mental Health, ³Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health

**Background:** Patients with MDD have clinically relevant, significant decreases in bone mineral density and experience increased fracture rates. RANKL is the principal osteoclastogenic factor, OPG is a decoy receptor for RANKL, and OPN plays a significant role in bone strength. We aimed to determine the OPG/RANKL and OPN levels and anti-suicidal effects in depressed adults. There are few case reports and no prospective controlled trials of ketamine for the treatment of adolescent MDD.

**Methods:** We are conducting a midazolam-controlled crossover trial to evaluate the effects of ketamine in treatment-refractory adolescent MDD over four weeks. Adolescents must have failed at least one adequate trial of a standard antidepressant to enroll. Adolescents seeking ketamine treatment who do not meet inclusion criteria are referred to our Interventional Psychiatry Service on a case-by-case basis.

**Results:** We report a case of successful treatment of an adolescent with severe, medication-refractory MDD with suicidality who did not meet trial criteria, but was treated with ketamine through our interventional service. We demonstrate a rapid reduction of depressive symptoms (via CDRS and MADRS), suicidality (via SSI), and hopelessness (via BHS) that was sustained with a multiple infusion paradigm. Trial enrollment is ongoing.

**Conclusions:** Given the potential therapeutic benefits of ketamine and the burden of treatment-refractory adolescent MDD, ketamine deserves further study as a potential treatment in adolescents in appropriately supervised settings and with informed consent.

**Supported By:** Yale Child Study Center Pilot Award; AACAP Pilot Award

**Keywords:** Ketamine, Adolescent Depression, Suicide, Antidepressant, Glutamate
**Saturday Abstracts**

**1004. Clinical Predictors of an Antisuicidal Response to Ketamine**

Julia Yarrington, Elizabeth Ballard, David Luckenbaugh, Mark Niciu, Marc Lener, Bashkim Kadiu, Lawrence Park, and Carlos Zarate

National Institute of Mental Health

**Background:** Suicide is one of the leading causes of death in the United States. Despite treatment efforts, the national suicide rate has increased in recent years. Currently, there are no pharmacological treatments for suicidal ideation (SI). For individuals experiencing a suicidal crisis, rapid acting medications may save lives. Recent studies suggest ketamine, a glutamate modulator, elicits rapid antisuicidal responses. We examined clinical factors that might predict ketamine’s antisuicidal response as a step towards understanding ketamine’s mechanism of action on suicidal thoughts.

**Methods:** The present study used data from patients experiencing SI (n=85), in clinical trials of ketamine in inpatients with treatment-resistant DSM-IV-TR-diagnosed unipolar or bipolar depression. Participants received one subanesthetic (0.5mg/kg) ketamine infusion over 40 minutes. SI was analyzed at one day post-ketamine infusion. We performed chi-square tests of independence between antisuicidal responders and non-responders using the Hamilton Depression Rating Scale (HDRS) suicide item.

**Results:** At one day post-infusion, previous psychiatric hospitalizations (p = .04), history of sexual abuse (p = .04), and family history of alcohol abuse (p = .02) were associated with an anti-suicidal response to ketamine, as was a trend in family history of suicide attempts (p = .055).

**Conclusions:** This study presents potential clinical predictors of antisuicidal ketamine response, demonstrating the possibility of identifying antisuicidal responders to ketamine. These predictors may both overlap and diverge from ketamine’s antidepressant response. These findings could be integrated with other efforts to advance predictive capacity for personalized treatments for SI. Further investigation of clinical predictors is essential to both improving patient care and better understanding the neurobiology of suicide.

**Supported By:** NIMH Intramural Program

**Keywords:** Ketamine, Suicide, Depression

**1005. Pre-Treatment Allostatic Load and Metabolic Dysregulation Predict Antidepressant Response in Major Depressive Disorder**

Christina Hough1, Alexandra Morford1, Elissa Eipel1, Daniel Lindqvist2, Francesco Saverio Bersani3, Felipe Jain1, Laura Mahan1, Rebecca Rosser1, Heather Burke1, Synthia Mellon1, Owen Wolkowitz1, and Victor Reus1

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**Background:** Major depressive disorder (MDD) is associated with significant health risks, including increased rate of cardiovascular disease, stroke, and diabetes. Allostatic load (AL), a biological measure of cumulative stress, and metabolic dysregulation (MetD), a summary score of metabolic syndrome risk factors, are associated with increased disease burden and mortality risk. Though increased AL and MetD are well-established in MDD, no prior study has prospectively examined their relationship with antidepressant response.

**Methods:** We determined baseline AL and MetD summary scores in 34 medically-healthy, medication-free individuals with MDD, before they completed eight-weeks of open-label selective serotonin reuptake inhibitor (SSRI) treatment, and in 67 healthy controls. Baseline AL and MetD scores of “Responders” (≥50% improvement in depression severity ratings after treatment), “Non-responders” (<50% improvement in depression severity), and controls were compared.

**Results:** Baseline depression severity did not differ between Responders and Non-responders. Baseline AL and MetD scores were significantly higher in Non-responders compared to Responders (p=0.025 and 0.026, respectively) and controls (p=0.039 and 0.001, respectively), but did not significantly differ between Responders and controls (p=0.512 and 0.748, respectively). Further, higher baseline AL and MetD were significantly associated with less absolute improvement in depression severity (p=0.010 and 0.011, respectively). Correcting for sex and age did not alter these findings.

**Conclusions:** Increased pre-treatment AL and MetD predicted poorer SSRI-response in MDD. This suggests that greater biological dysfunction (i.e. AL and MetD) may not only be associated with MDD, but may also relate to the capacity for clinical response to SSRI-treatment. Potential mechanisms of this relationship are discussed.

**Supported By:** RO1

**Keywords:** Major Depression, Metabolic syndrome, Allostatic Load, Treatment Response, Treatment predictions
1006. Effects of Modafinil on Emotional Processing in Patients with Remitted Depression

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1University of Cambridge, Dept of Psychiatry, 2Manchester University, Division of Neuroscience and Experimental Psychology, 3Norfolk and Suffolk NHS Foundation Trust, 4North Essex NHS Foundation Trust, 5Cambridgeshire and Peterborough NHS Foundation Trust, 6Cambridge Cognition, 7University of Cambridge, Dept of Clinical Neurosciences

Background: Cognitive dysfunction in depression is an unmet treatment need. Cognitive deficits in depression tend to persist in remission, and are associated with poorer functional outcomes (McIntyre et al. 2013). Patients with depression have cognitive deficits in cold cognition and hot cognition (emotion-laden). Recently, we showed that modafinil can improve episodic memory and spatial working memory in remitted depressed patients (Kaser et al. 2016) In this report, we present the findings on the effects of modafinil on emotional processing in patients with remitted depression.

Methods: Fifty-eight patients with remitted depression participated in the study. A randomised double-blind, placebo-controlled, parallel groups design was used. Participants received either single-dose modafinil (200 mg) or placebo. Patients completed Faces Go/No-Go tasks from EMOTICOM neuropsychological battery (Bland et al., 2016). A negative emotional bias measure (sad targets with neutral distracters compared to patients receiving neutral distracters) using reaction times was used. Correct responses (hits) and false alarms were calculated as a measure of signal detection (d-prime).

Results: Patients receiving modafinil showed a greater negative emotional bias (t(56) = 2.20, p=0.032) which appeared to be driven by longer reaction times to sad faces with neutral distracters compared to patients receiving placebo. There were no significant differences between d-prime measures (p>0.05).

Conclusions: Modafinil led to slower responses towards sad faces indicating less negative bias in patients with remitted depression. This effect was independent of signal detection measures. Beneficial effects of modafinil on emotional processing suggested that modafinil can be used to address hot cognitive deficits associated with depression.

Supported By: MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute

Keywords: emotion, cognition, depression, neurocognitive, treatment

1007. Ketamine-Induced Dissociative Effect Associates with the Change of Mean Global Neuronal Activity

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Background: Ketamine-induced antidepressant effect has been reported in animal and human studies. The rapid efficacy of ketamine, a non-completive NMDA receptor antagonist, indicates different mechanisms compared to currently available drugs. However, the accompanying adverse effects and association to antidepressant properties remain unknown. This study investigated the change of mean global neuronal activity, also known as global signal (GS), 1h and 24h after ketamine infusion, and the relationship with the acute dissociative experience.

Methods: In a randomized, double-blind, placebo-controlled study, 81 healthy controls received single subanesthetic dose of ketamine (0.5 mg/kg within 40 min) or saline. For each subject, resting-state fMRI were acquired at baseline, 1h, and 24h post-infusion at 7T scanner. The dissociative side effects were evaluated using Clinician Administered Dissociative States Scale (CADSS) right after the infusion. EPI data were preprocessed using scripts from the 1000 functional connectome project (FCP, version 1.1-beta). GS was extracted and transformed into Z-Score, and its change was assessed by implementing Teager-kaiser operator. Thirty-two ketamine and thirty placebo subjects were tested at threshold p<0.05.

Results: Larger fluctuation of GS was found 1 hour after ketamine administration (t=2.09, p=0.04). Moreover, in ketamine group, the GS at 1 hour associated with total CADSS (r = −0.353, p=0.04), more specifically with subscale derealization (r = −0.466, p = 0.007).

Conclusions: GS changes and associated adverse effects were observed only in the acute phase after ketamine administration. This could imply that long-term antidepressant results are downstream effects from the acute phase, and GS can be seen as an early marker of underlying neuronal activity induced by ketamine.

Supported By: SFB; DFG

Keywords: Ketamine, Resting state fMRI, Global signal, Dissociative effect

1008. Population Pharmacokinetic Analysis and Simulations of a Two Month Dose Interval Regimen for Aripiprazole Lauroxil

Marjie Hard1, Richard Mills2, Brian M Sadler2, and Lisa von Molke1

1Alkermes, Inc, 2Icon

Background: Aripiprazole lauroxil (AL) is approved for the treatment of schizophrenia (SCZ) with once-monthly and once every 6 weeks dosing intervals. A new dose (1064 mg) intended to extend the dose interval to every 8 weeks was evaluated in a Phase 1 PK study and using PK modeling.

Methods: The PK study evaluated three AL dosing intervals, including every 8-weeks, in n=139 subjects with stable SCZ. The results of the study were combined with data from 4 prior clinical PK studies (n=561) to update an existing population PK (PopPK) model. Aripiprazole concentrations from the
8-week regimen were compared to the 4- and 6-week regimens. The impact of missed doses and re-initiation of treatment with AL following a delay in dosing were also assessed.

**Results:** As determined in the clinical study and through model-based simulations, 1064 mg every 8-weeks yielded aripiprazole concentrations that were within the aripiprazole exposure range associated with clinically effective and well-tolerated doses of AL. Median steady-state concentrations of aripiprazole for the 8-week regimen from the model were comparable to the 882 mg every 6 week and 662 mg monthly regimens (154 ng/mL, 165 ng/mL, and 183 ng/mL, respectively). Aripiprazole concentrations declined slowly when the scheduled dose was delayed by up to 2-weeks (<20%), and readily returned to expected levels when AL dosing was resumed.

**Conclusions:** AL 1064 mg administered every 8-weeks resulted in aripiprazole concentrations within the AL approved monthly dose range, indicating that AL 1064 mg may be suitable for a two month dose interval.

**Supported By:** Alkermes, Inc. Waltham, MA, USA

**Keywords:** Schizophrenia, Computational Modeling, Pharmacokinetics, Steady-state

**1009. Oxytocin Enhances Overbidding in Multiplayer Auctions**

Ellen Bradley,1 and Johanna Brustkern,2, Lize De Coster,1, Woutervan den Bos,3, Samuel McClure,4, and Josh Woolley1,5,*

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**Background:** Decision-making in dynamic social contexts requires multiple cognitive abilities, including mentalizing, that are frequently impaired in schizophrenia. Oxytocin administration has been shown to improve mentalizing in schizophrenia, suggesting therapeutic potential.

**Methods:** To better understand social decision-making in schizophrenia and oxytocin effects on social-decision making, we administered one dose of oxytocin (400U) or placebo to 39 male participants with schizophrenia and 54 matched controls in a randomized, double-blind study. Participants completed a multiplayer auction task known to induce the “winner’s curse,” i.e., overbidding in order to win, despite financial losses. We analyzed bidding behavior over 35 trials using multilevel linear mixed models, and performance on a control non-social risk-taking task using mixed-factorial ANOVA.

**Results:** We found an effect of Trial, p<0.001, but not Group or Drug. We also found DrugXTrial, p=0.054, and GroupXTrial, p<0.05, interactions, which were due to sustained overbidding in the oxytocin condition and in individuals with schizophrenia. Indeed, oxytocin was associated with an increase in the winner’s curse, with participants accepting greater financial losses in the oxytocin condition (M = $11.04, p = 0.07). There was no effect of Group or Drug on non-social risk-taking behavior.

**Conclusions:** Consistent with findings that oxytocin improves mentalizing, higher bidding in the oxytocin condition may reflect an increased social reward from winning the auction despite losing money. Additionally, individuals with schizophrenia may be more susceptible to the winner’s curse, possibly due to impaired reinforcement learning. Using neuroeconomic tasks can help to clarify mechanisms underlying altered social decision-making and the effects of oxytocin in schizophrenia.

**Supported By:** Career Development Award CX000758 (Josh Woolley) from the United States Department of Veterans Affairs, Office of Research and Development, Clinical Science Research and Development program

**Keywords:** Schizophrenia, Oxytocin, Mentalizing, Neuroeconomics
**Background:** Elevated heart rate is strongly associated with mortality in the general population. Tachycardia is also a known adverse effect during clozapine treatment. However, prevalence reported differs widely between studies and hitherto there are no studies comparing clozapine treated patients with a similar control group. The present study was carried out to assess the prevalence of tachycardia in patients treated with clozapine and antipsychotic long-acting injections (LAI).

**Methods:** Data on heart rate (HR), smoking, concomitant medication and relevant anthropometric and laboratory measurements including thyroid hormones and hemoglobin levels were collected for all clozapine treated patients (n=174) in a defined catchment area and compared with data on patients treated with LAI (n=87). Student’s t-test, Pearson correlation and Chi2-tests were used for statistical calculations.

**Results:** 33% of patients on long-term clozapine treatment had a resting state tachycardia (HR>100) compared with 16% in the LAI group (p<0.001). Mean HR was 91 in the clozapine group and 82 in the LAI group (p<0.001). Clozapine dose correlated with HR. The majority of patients with HR>100 had no specific treatment for tachycardia.

**Conclusions:** In conclusion, the prevalence of resting state tachycardia was twice as high in patients treated with clozapine, as in a similar patient group with severe schizophrenia spectrum disorder. The tachycardia was in many cases clinically unnoticed. Tachycardia during clozapine treatment is thus a common phenomenon that must be actively monitored for and when noticed, further investigated and treated.

**Keywords:** Schizophrenia, Clozapine, Tachycardia, Long acting injectable, Adverse Effects

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**1012. The Relationships of the Pharmacokinetics of TAK-063 to the Cognitive and Mood Effects of the Compound in a Multiple Dose, Phase 1 Study in Healthy Japanese Subjects and Subjects With Schizophrenia**

Tom Macek1, Maggie McCue1, Paul Goldsmith2, Jinhui Xie1, John Affinito1, and Keith Wesnes3

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**Background:** In a phase 1 multiple dose trial, the phosphodiesterase inhibitor TAK-063 produced a range of disruptions of cognitive function and mood in both healthy Japanese subjects (HJS) and subjects with stable schizophrenia spectrum disorder. The tachycardia was in many cases clinically unnoticed. Tachycardia during clozapine treatment is thus a common phenomenon that must be actively monitored for and when noticed, further investigated and treated.

**Methods:** Cohorts of HJS received TAK-063 orally for 7 days at doses of 3, 10, and 20 mg; cohorts of SSS received 3, 10, 20, 30, and 100 mg. Cognitive function was assessed with the CDR System together with self-ratings of alertness and mood. The Cmax and AUC24 levels appeared to be associated with changes in cognition and mood on days 1 and 7.

**Results:** On day 1 for both populations, the increases in exposure with increasing dose were associated with disruptions of various aspects of cognition, alertness, and mood; this profile was more marked and widespread in the HJS. On day 7, these correlations all reduced in magnitude and statistical reliability for both populations. However, for the HJS, a new PK association appeared for disruption of postural stability. In contrast, for the SSS on day 7, higher plasma levels appeared to be associated with improvements in speed of retrieval from both working and episodic memory.

**Conclusions:** In both populations, disruptions of cognition and mood with TAK-063 correlated with increasing exposure, most notably on day 1. On day 7, in SSS, a positive association between plasma TAK-063 and improved speed of memory retrieval was identified.

**Supported By:** Sponsored by Takeda Development Center Americas, Inc., Deerfield, IL, USA.

**Keywords:** Schizophrenia, cognition, Phase I, PK-PD relationships, PDE10A inhibitors
1014. Network Diagnoses – Diagnosing Networks: Classification of Schizophrenia, Parkinson and Aging

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Background: Neuroimaging-based diagnostic to discriminate patients from healthy controls or old from young participants has gained increasing importance. Here, we assessed, whether specific functional networks are differentially altered in Schizophrenia (SCZ), Parkinson Disease (PD) and Healthy Aging (HA), and hence, enable network-based diagnoses.

Methods: Support vector machine (SVM) classification of SCZ, PD and HA based on distinct functional networks in large multi-site samples (86 SCZ, 80 PD, 95 old participants; matched controls). We investigated 14 functional networks robustly defined by quantitative meta-analyses reflecting a broad set of cognitive, social-affective and motor functions. To examine whether connectivity within a network contains predictive information on the respective groups linear two-class SVMs were computed and evaluated based on 25 replications of a nested 10-fold cross validation scheme.

Results: For SCZ the combination of the Working Memory and Default Mode networks (Acc=74%), Emotional processing (Acc=72%) and Empathy (Acc=71%) yielded the best accuracy. For PD networks underlying Autobiographical Memory (Acc=75%), Cognitive Action Control (Acc=74%) and Reward processing (Acc=71%) provided the best classification. None of these networks discriminated the respective other disorder. This differentiated picture contrasted markedly with age-classification where each network yielded accuracies ≥74%, outperforming all clinical classifications.

Conclusions: Our approach allows inference on the amount of disease-or age-specific information in different mental systems. Both SCZ and PD were specifically predicted by networks that resonate well with known clinical and pathophysiological features. In turn, the high performance of all networks for age-classification highlights the importance of considering age-related effects in clinical classification studies.

Supported By: German Research Council; European Commission; NIH

Keywords: Schizophrenia, Parkinson’s disease, Aging, classification, Brain networks


Hugo Geerts and Athan Spiros

In Silico Biosciences

Background: Increasing clinical evidence, including ketamine studies in healthy volunteers, suggests that early psychosis is different from chronic schizophrenia. We explored the use of Quantitative Systems Pharmacology, an advanced computer modeling platform formally integrating available domain expertise that was able to better predict clinical outcomes in a number of cases.

Methods: The cortico-striatal-thalamo-cortical closed network computer model consists of 116 neurons (8 different cell types) based on human neuro-anatomy and neurophysiology with the physiology of 35 CNS targets implemented. Previously, using a pathological environment associated with chronic schizophrenia, we achieved a high correlation between a Shannon entropy outcome in the thalamus and clinical changes on PANSS Total for 88 different drug-dose interventions, including augmentation trials.

Results: The model recapitulates the observed cognitive outcome, EEG and BOLD fMRI changes after ketamine in healthy volunteers, and generated a 5 points worsening on the PANSS Total clinical scale. Using the same Shannon entropy outcome, the cortical excitation-inhibition dysfunction (decreases in NMDA and AMPA conductance of 5% and 3% and 15% on GABA conductance of interneuron-interneuron synapses) generated a similar outcome to a chronic untreated schizophrenia patient without substantial changes in striatal dopamine. Decreasing Pyramidal-thalamic and increasing MSN -GPi (direct pathway) or decreasing STN-GPi connections also worsens outcome, but combination of the two sets was not additive. Antipsychotics can reverse the system back to normal but not to the same degree as in chronic schizophrenia.

Conclusions: Quantitative Systems Pharmacology is a possible tool to generate experimentally testable hypotheses about the generation of psychotic symptoms in early psychosis.

Keywords: Early psychosis, Basal Ganglia, Quantitative Systems Pharmacology, Computational Modeling

1016. The Functional Connectivity Modeling of Human Striatum and the Altered Functional Connectivity of Striatum Subregions in First-Episode Schizophrenia

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Background: Striatum involves in diverse psychological process and plays a central role in the dysfunctions of schizophrenia. However, as a heterogeneous complex structure, the precise connectivity profile of human striatum remains unclear. Recently, Tziortzi (2014) subdivided the striatum into seven subregions and made a striatal structural connectivity atlas according to their DTI and PET study.

Methods: We used the meta-analytic connectivity modeling (MACM) to determine consistent functional coactivation patterns across experiments and behaviors associated with the seven striatal subregions defined by Oxford–GSK–Imanova Striatal connectivity Atlas (Tziortzi, 2014), along with a cross validation using the same seven ROIs for resting-state FC (RSFC) analysis on 27 healthy subjects. Then we compared RSFC of those seven striatal subregions between 45 first-episode, treatment-naive patients with schizophrenia and those 27 healthy controls.

Results: 1) MACM results showed good consistency between functional and structural connectivity maps in Limbic, Executive, Rostral-motor, Caudal-motor, and Partiela striatal subregions. For example, Str_limbic subregion showed strong FC with mPFC and IFG, and was involved mainly in cognition and emotion behavior domains and reward paradigms. 2) There was high concordance among the RSFC maps of and the MACM results on seven striatal subregions. 3) Comparing to HC, significantly reduced FC between the Str_limbic subregion and thalamus/mPFC/IFG/insula, and Str_executive subregion and thalamus/SLA were identified in the FES group (FWE, p<0.05).

Conclusions: We demonstrate consistent coactivation maps across experiments and behaviors for different anatomical striatal subregions, which further validated by the RSFC analysis. Those findings help us to explain the neural functional deficit of FES.

Supported By: NSFC (31671144 , 61473221); NCET-12-0557
Keywords: striatum, first episode schizophrenia, Meta-analytic Connectivity Modeling (MACM), Functional connectivity, BOLD fMRI

1018. Modeling Hierarchical Heterogeneity of Cortical Circuits in Large-Scale Networks with Relevance to Functional Dysconnectivity in Schizophrenia
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Background: Computational models of large-scale brain networks provide a useful tool to study relationships between hypothesized microcircuit dysfunction in neuropsychiatric disorders, and systems-level observations from non-invasive neuroimaging techniques such as fMRI. Previously, we found that pattern of altered resting-state functional connectivity (rs-FC) in schizophrenia shows heterogeneity related to cortical hierarchy (Yang GJ et al., 2016, PNAS). These findings highlight a need to extend computational frameworks, which typically assume microcircuit properties are homogenous across cortex, to incorporate hierarchical heterogeneity.

Methods: We investigated effects of cortical heterogeneity on large-scale neuronal dynamics using a biophysically-based computational model and neuroimaging data from the Human Connectome Project. Specifically, we characterized roles of heterogeneity in NMDA conductance of local and long-range inputs along cortical hierarchy. We used the MRI-derived myelin map as a proxy measure for cortical hierarchy. Based on similarity between simulated and empirical rs-FC, we estimated optimal gradients for NMDA conductance across cortical hierarchy.

Results: We found that microcircuit heterogeneity substantially increased the fit of the model to empirical rs-FC. The optimal heterogeneity gradients for the computational model revealed...
1019. The Association between Scholarly Impact and Canadian Institutes of Health Research Funding in Psychiatry

Frank MacMaster¹, Rose Swansburg¹, and Katherine Rittenbach²

¹University of Calgary, ²Strategic Clinical Network for Addictions and Mental Health

**Background:** Research productivity is commonly measured by bibliometrics and the procurement of funding from external agencies, such as the Canadian Institute of Health Research (CIHR). Here, we examine the association between scholarly impact and CIHR awards to psychiatry faculties in Canada.

**Methods:** Faculty lists were acquired online. The sample included 1,602 participants (assistant professors = 911, associate professors = 388, full professors = 303). Names were searched via Web of Science for their corresponding h-index and total citations. This was cross-referenced against department of psychiatry and operating/foundation grant set as the search term.

**Results:** As measured by h-index, CIHR-supported faculty (principle investigator) had a greater scholarly impact than their non-CIHR-supported peers (p < 0.001). This was also true for the total number of citations (p < 0.001). The amount of CIHR support garnered by an investigator was correlated with the h-index and total citations. However, there are 2.62 investigators of hierarchical patterns of dysconnectivity in neuropsychiatric disorders.

**Supported By:** Swartz Foundation; BlackThom Therapeutics; NIMH (1R01MH108590-01)

**Keywords:** Resting state fMRI, Computational Neuroscience, Computational Psychiatry, NMDAR hypofunction, Schizophrenia

1020. Psychiatry Resident and Program Director Perceptions of Neuroscience and Research Activity

Frank MacMaster¹, Jordan Cohen¹, Waqar Waheed¹, Emilie Magaud¹, Rose Swansburg¹, and Katherine Rittenbach²

¹University of Calgary, ²Strategic Clinical Network for Addictions and Mental Health

**Background:** Research activity is especially critical in the field of psychiatry as it is evolving rapidly thanks to advances in neuroscience. The goal of this survey was to gain an understanding of perceptions and experiences of both neuroscience and research, for psychiatry residents and program directors.

**Methods:** We administered a 64-item survey regarding research experiences targeted at psychiatry residents and postgraduate residency program directors in Canada.

**Results:** One hundred and nineteen participants answered the survey (16 program directors, 103 residents) allowing for a margin of error of 8.4% at a 95% confidence interval. Research was rated as important in informing clinical practice (87.0%), but only 28.7% of respondents reported that it was taught well at their home institution. Only a small proportion was enthusiastic or very enthusiastic about participating in research (21.7%). Half of respondents felt they were receiving adequate training in neuroscience with most reporting opportunities to participate in neuroscientific research. However, few felt (33%) prepared to translate neuroscientific findings into practice. Almost half of participants indicated that the Royal College should develop a specific neuroscience curriculum.

**Conclusions:** While the importance of research is recognized, there is little consensus with respect to whether a standardized research practicum component is included in the resident curriculum. In addition, findings do support the idea that changes are needed to improve neuroscience literacy among residents in psychiatry.

**Supported By:** Strategic Clinical Network for Addictions and Mental Health

**Keywords:** Residency, Neuroscience, Research Domain Criteria (RDoC), Research
and Surgeons, Department of Psychiatry, Yale University School of Medicine, Western Psychiatric Institute and Clinic

**Background:** Despite exponentially increased knowledge of the neuroscientific basis of psychiatric disorders and treatments, clinical practice does not routinely employ this information, obscuring the utility of neuroscience education for psychiatry trainees. One potentially beneficial but largely unexplored use of neuroscience material is patient education. We sought to determine whether patients found it helpful to discuss the neuroscience basis of their disorders and treatment plan in a structured group therapy format, and moreover, whether patients could gain an appreciation for this material in such a setting.

**Methods:** Participants included a total of 32 patients with co-occurring substance use and mood or psychotic disorders enrolled in the Intensive Outpatient Program at the Center for Psychiatry and Chemical Dependency Services of WPIC. The neuroscience content presentation, derived from the “Talking Pathways to Patients” National Neuroscience Curriculum Initiative module, included 30 minutes outlining neural pathways of reward/addiction followed by 30 minutes Q&A, delivered by a medical student to groups of 8-15 patients. A brief questionnaire assessed whether patients found the content accessible and helpful.

**Results:** On Likert scales with a possible range of 1-5, patients rated their level of understanding of the material at $4.36 \pm 0.79$ and reported that they found it helpful at a level of $4.20 \pm 0.74$.

**Conclusions:** These data suggest that patients find benefit in receiving information on the neuroscience basis of their psychiatric disorders and treatment. Moreover, these results provide clinical justification to explore further whether delivering patient education in a structured group setting could be a valuable learning tool for trainees.

**Supported By:** F30 MH105199; R25 MH101076-02S1

**Keywords:** education, Addiction, Neuroscience training, Individualized Treatment

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**LATE BREAKING POSTER SESSION**
Saturday, May 20, 2017, 5:00 PM – 7:00 PM

**Late Breaking Poster Session**

The Late Breaking poster abstracts were accepted after this supplement was published. See the On-Line Program Planner or Mobile App for the complete abstract.
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