Abstracts

Society of Biological Psychiatry 2015 Annual Meeting

THURSDAY, MAY 14

PLENARY SESSION
Anxiety and Fear
Thursday, May 14, 2015, 8:05 AM – 11:30 AM
Canadian – Convention Floor
Chair: Amit Etkin

1. Coming to Terms with Fear

Joseph LeDoux

Center for Neural Science, New York University, New York, NY

Fear is a fundamental part of human life, and plays a central role in psychiatric disorders. One of the main ways that fear has been related to brain mechanisms is through studies of Pavlovian fear conditioning. Research on Pavlovian fear conditioning has been very successful in revealing the brain's so-called fear system. The field has now matured to the point where a sharper conceptualization of what is being studied could be very useful as we go forward. Terms like "fear conditioning" and "fear system" blur the distinction between processes that give rise to conscious feelings of fear and non-conscious processes that control defense responses elicited by threats. The fear conditioning procedure allows exploration of how the brain learns about and later detects and responds to threats, not how the brain feels fear. While mechanisms that detect and respond to threats contribute indirectly to conscious feelings of fear, they are not the same as those that give rise to conscious fear. This is an important distinction since symptoms based on conscious and non-conscious processes may be vulnerable to different predisposing factors and may also be treatable with different therapeutic approaches in people who suffer from uncontrolled fear or anxiety. A conception of aversive conditioning in terms of circuits that detect and respond to threats non-consciously, but that contribute to conscious fear, is proposed as way forward. Key to this conception is a new set of terms that avoid the implication that the circuits are responsible for conscious feelings of fear. Thus, circuits that detect and respond to threats are conceived as defensive survival circuits; these work non-consciously in humans and other animals. Activation of defensive survival circuits results in the expression of defensive responses in the body, and a hosts of changes in the brain. Within the brain, the collective consequence of activating a defensive survival circuit is the establishment of a *defensive motivational state.* This global state organizes future brain functions, including actions, but also functions non-consciously. In species with the cognitive where-with-all to be able to monitor brain activities in relation to the self, a conscious feeling of fear can arise from the coalescence in awareness of (a) sensory information about an external stimulus; (b) long-term semantic and episodic memories that identify the present stimulus as a threat to one's self, and (c) cognitive monitoring of defensive motivational state information triggered within the brain and in external behavior. The nervous systems of many organisms create these global motivational states that are part of the quest to survive dangeer. Only an organisms that can be conscious of its own brain's activities in relation to a sense of self can consciously experience fear when a defensive motivational state is helping it to stay alive.

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2. Optical Tools for Probing Intact Biological Systems

Karl Deisseroth

Bioengineering, Stanford University, Stanford, CA

Over the past decade we have developed both optogenetics (a technology for precisely controlling millisecond-scale activity patterns in specific cell types using microbial opsin genes and fiberoptic-based neural interfaces1,2) and CLARITY (a technology to optically resolve high-resolution structural and molecular detail within intact tissues without disassembly). Most recently in optogenetics, we have developed strategies for targeting microbial opsins and light to meet the challenging constraints of the freely-behaving mammal, engineered a panel of microbial opsin genes spanning a range of optical and kinetic properties, built high-speed behavioral and neural activity-readout tools compatible with real-time optogenetic control, and applied these optogenetic tools to develop circuit-based insight into anxiety, depression, and motivated behaviors3,4. Distinct from optogenetics, CLARITY5 can be used to transform intact biological tissue into a hybrid form in which components are removed and replaced with exogenous elements, resulting in a transparent tissue-hydrogel that both preserves, and makes accessible, structural and molecular information for visualization and analysis. With CLARITY, whole mouse brains have now been labeled and imaged, and molecular markers have been used to identify individual structures and projections in banked human brain tissue, thereby unlocking rich sources of information for probing disease mechanisms as well as the native structure and complexity of the nervous system5, in a manner complementary to new optogenetic approaches for control and observation of activity in the setting of psychiatric disease-related behaviors6-8.

References

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3. Genetic and Epigenetic Approaches to Fear and Extinction: From Bench to Bedside

Kerry Ressler[1,2]

[1]Psychiatry and Behavioral Science, Emory University, Atlanta, GA, [2]Howard Hughes Medical Institute, Atlanta, GA

Fear-related disorder such as post-traumatic stress disorder, panic disorder and phobia manifest in ways that are consistent with an uncontrollable state of fear. Their development involves heredity, previous sensitizing experiences, association of aversive events with previous neutral stimuli, and inability to inhibit or extinguish fear after it is chronic and disabling. I will highlight recent progress in fear learning and memory, differential genetic susceptibility to disorders of fear, and how these findings are being applied to the understanding, treatment and possible prevention of fear disorders. Promising advances are being translated from basic science to the clinic, including approaches to distinguish risk versus resilience before trauma exposure, methods to interfere with fear development during memory consolidation after a trauma, and techniques to inhibit fear reconsolidation and to enhance extinction of chronic fear. Cutting edge approaches to understand the genetic and epigenetic regulation at a cell-type specific level within amygdala, medial prefrontal, and hippocampal circuitry as it relates to fear extinction will also be discussed. It is hoped that this new knowledge will translate to more successful, neuroscientifically informed and rationally designed approaches to disorders of fear regulation.

References

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4. The Prevention and Treatment of PTSD Based on Learning Theory

Barbara O. Rothbaum

Trauma and Anxiety Recovery Program, Emory University School of Medicine, Atlanta, GA

Unlike other psychiatric disorders, the precipitant for adult posttraumatic stress disorder (PTSD) is a known event, allowing for immediate intervention, presenting the potential to prevent, and ultimately eliminate for many, the occurrence of this most serious condition. The evidence from animal studies suggests that immediate extinction training (10 min after conditioning) was more effective on spontaneous recovery, renewal, and reinstatement than later extinction training (72 hours). This knowledge of the precipitant combined with excellent animal models of fear memory consolidation and the ability to interrupt this consolidation in the early post-trauma-exposure period, has led to the exciting possibility that interventions in the immediate aftermath of trauma could potentially prevent the development of PTSD. In our completed pilot work, an early exposure-based intervention begun within hours of trauma exposure significantly decreased PTSD and depression 1- and 3-months post-trauma compared to those who did not receive the intervention and seemed to mitigate a genetic risk for PTSD. We will then turn to learning theory in approaches to treat chronic PTSD. Exposure therapy involves repeated therapeutic activation of the trauma memory that allows new information to be encoded, thus reducing the memory-associated fear and anxiety. D-cycloserine is an N-methyl-D-aspartate glutamate (NMDA) receptor partial agonist shown to improve the efficacy and durability of exposure therapy when dosed acutely prior to treatment for several anxiety disorders. A recent study to determine the effectiveness of Virtual Reality Exposure augmented with D-cycloserine (50mg) or alprazolam (0.25mg), compared to placebo, in reducing PTSD due to military trauma in Iraq and Afghanistan will be presented. Benzodiazepine use during treatment impaired recovery, and D-cycloserine enhanced VRE in patients who demonstrated within-session learning. D-cycloserine augmentation treatment in PTSD patients reduced cortisol and startle reactivity compared to the alprazolam and placebo treatment, consistent with the animal literature.

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LUNCH AND LEARN
Thursday, May 14, 2015 – 11:40 am – 12:20 pm
Territories – Main Mezzanine
Chair: Paul Holtzheimer
Co-Chair: Kristina M. Deligiannidis

5. Getting Published

John Krystal

Dr. John Krystal, Editor of Biological Psychiatry, will describe how the journal reviews and selects papers, what kinds of features help papers to be published, and what pitfalls to avoid. Suggestions will include how to respond to reviewers and editors, why you should review as well as submit papers, and how avoid having your paper triaged.

6. Working with the NIH

Charles B. Nemeroff

The process of applying for NIH funding is complex and working with program staff at the NIH can be helpful. Investigators should consider working with the project officer from very early on to determine if the grant idea is in alignment with the NIH strategic plan. Similarly, project officers can be helpful in reviewing drafts of specific aims and giving feedback. Also, in preparing to respond to the council, the project officer can be of assistance in crafting a compelling argument for funding. The project officer can be a resource for providing on-going feedback/guidance and who will help shepherd a project from cradle to funding.

SYMPOSIUM
Beyond PGC2: Mechanisms for Genetic Variation that Increase Risk for Schizophrenia
Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Canadian – Convention Floor
Chair: Joel E. Kleinman

7. Modeling a Genetic Risk for Schizophrenia in iPSC Reveals Neural Stem Cell Deficits

Guo-li Ming

Department of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Defects in brain development are believed to contribute toward the onset of neuropsychiatric disorders, but identifying specific underlying mechanisms has proven difficult.
Methods: We have derived human iPSC from patients carrying 15q11.2 microdeletion and found that iPSC-derived neural progenitors with the microdeletion exhibit deficits in adherens junctions and apical polarity.
Results: Further experiments suggest that these deficits results from haploinsufficiency of CYFIP1, a gene within 15q11.2 that encodes a subunit of the WAVE complex, which regulates cytoskeletal dynamics. Targeted human genetic association analyses revealed an epistatic interaction between CYFIP1 and WAVE signaling mediator ACTR2 and risk for schizophrenia.
Conclusions: Our findings provide insight into how CYFIP1 regulates neural stem cell function and may contribute to the susceptibility of neuropsychiatric disorders.

Keywords: iPSC, schizophrenia, CNV, CYFIP1
Supported by: MSCRF

8. Functionally Mapping Clinical Risk SNPs for Schizophrenia to Local Expression Levels in Human Frontal Cortex

Andrew E. Jaffe

Clinical Genetics, Lieber Institute for Brain Development, Baltimore, MD

Background: 108 genetic loci have now reached "genome-wide" significance for clinical association with schizophrenia, utilizing 37k cases and 113k controls [O'Donovan et at, Nature 2014]. However, these loci span ~21Mb and contain 331 RefSeq genes across 1154 transcripts (574 genes across 1884 transcripts within +/- 100kb).
Methods: We performed genotyping and RNA sequencing in dorsolateral prefrontal cortex (DLPFC) tissue from 238 adult non-psychiatric controls (age > 13) and 51 fetal subjects. We evaluated the association of clinical risk SNPs in the 108 loci on nearby gene expression levels across various summarizations using an expression quantitative trait loci (eQTL) framework.
Results: We identified significant genetic control of nearby expression for 64 of the GWAS-positive loci at any gene expression summarization level (gene, exon or junction) in the adult subjects – only 26 of these loci are associated with expression across all three summarization levels. Junction-level analyses identified a subset of loci where the risk variant only associates with a single transcript within 1 megabase of the risk variant, including potentially novel transcripts not present in the current Ensembl annotations.
Conclusions: We have identified the likely candidate gene for a subset of schizophrenia-associated genetic risk loci based on associations with nearby gene expression levels in the transcriptomes of non-psychiatric controls.

Keywords: RNA sequencing, expression quantitative trait loci (eQTL), postmortem human brain tissue, gene expression, functional genomics

9. Selective Effects of the GWAS DRD2 Locus Associated with Schizophrenia on the Prefrontal-nigro-striatal Circuits Supporting the Executive Functions

Eugenia Radulescu[1], Qiang Chen[1], Venkata S. Mattay[1], Joseph H. Callicott[2], Caroline F. Zink[1], Terry E. Goldberg[3], Gianluca Ursini[1], Joel E. Kleinman[1], Daniel R. Weinberger[1]

[1]Clinical Sciences Division, Lieber Institute for Brain Development, Baltimore, MD, [2]Clinical Brain Disorders Branch, National Institute of Mental Health/ National Institutes of Health, Bethesda, MD, [3]The Litwin-Zucker Research Center, The Feinstein Institute for Medical Research, Manhasset, NY

Background: A locus overlapping the DRD2 gene- the archetypical antipsychotic target, was among the 108 loci significantly associated with the schizophrenia risk in the GWAS recently published by the Psychiatric GWAS Consortium [doi:10.1038/nature13595]. Our multi-task fMRI study explored DRD2 (rs6589377-proxy of rs2514218) effects on fMRI phenotypes related to cortico-nigro-striatal circuits.
Methods: Healthy controls (NHC=51-239) and individuals with schizophrenia (NSCZ=30-60) (Caucasians), genotyped for rs6589377, performed various cognitive tasks during fMRI. Functional MR images were analyzed with the Statistical Parametric Mapping software. Rs6589377 effects on activation and connectivity (psycho-physiological interaction-PPI) were evaluated.

Further, the interaction between rs6589377 and neuroleptic exposure on brain functionality, was examined in a schizophrenia sample (N=57).
Results: The data suggest relative specificity of DRD2 effects on the prefrontal- nigro-striatal circuits sub-serving working-memory and mental effort. We found rs6589377 significantly associated with brain activation during working memory paradigms ('nback' [Callicott et al 2003] in R-DLPFC/ BA9, p<0.001, Z-score=4.25, in HC and SCZ and during 'updating' [doi:10.1016/j.neuroimage.2011.05.006] in Substantia-Nigra, p<0.001, Z-score=3.37). PPI analysis showed a DRD2 association with coupling between R-DLPFC- right caudate (Z=3.43; p<0.001) during 'nback'. Intriguingly, no DRD2 effect was significant on brain activation during episodic memory, response inhibition, reward anticipation. Genotype interacted with neuroleptic exposure on coupling between right DLPFC and right Caudate in the SCZ sample (p<0.001, Z-score=4.14).
Conclusions: Our findings support the role of the DRD2 locus variation on brain functionality and suggest relatively selective DRD2 effects on the cortico-nigral rather than striatal activity, worth exploring for new therapeutic pathways.

Keywords: DRD2, fMRI, cortico-nigro-striatal circuits, working memory, connectivity

10. GWAS Derived Risk Profile Score Is Associated with Schizophrenia Only in Individuals Exposed to Obstetric Complications

Gianluca Ursini[1,2], Stefano Marenco[3], Qiang Chen[1], Richard E. Straub[1], Giovanna Punzi[1,2], Daniel R. Weinberger[1]

[1]Division of Clinical Sciences, Lieber Institute for Brain Development, Baltimore, MD, [2]Group of Psychiatric Neuroscience, Dept. of Basic Medical Science, Neuroscience and Sense Organs, Aldo Moro University, Bari, Italy, [3]Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD

Background: Schizophrenia GWASs suggest that genetic risk is conferred by many small effect alleles(1). Obstetric and intrauterine complications(OCs) increase risk for schizophrenia(2). Here, we test whether risk profile scores(RPSs) constructed from alleles showing association with schizophrenia(1) interact with OCs in predicting case-control status.
Methods: 272 healthy subjects and 228 patients with schizophrenia were assessed for OC exposure, using the McNeil-Sjostrom Scale(2). RPSs were generated using odds ratios derived from the PGC2 datasets(1). Regression analyses were performed in 'R', with case-control status as dependent variable, and i)RPS, ii)OCs, iii)RPS, OCs and their interaction as predictors.
Results: All the RPSs generated using different threshold for selecting risk alleles predict case-control status without taking into account OCs(p<3.65e-06); OCs exposure alone does not predict case-control status. Strikingly, analysis of the interaction between OCs and the RPS obtained with the set of SNPs showing GWAS significant association with schizophrenia (p<5E-08, RPS1) show that OC exposure predicts case-control status(p=0.04), while RPS1 does not(p>0.34); moreover OCs and RPS1 significantly interact to predict case-control status(p<0.01), so that only in presence of OCs is the RPS1 associated with schizophrenia. No significant interaction(p>0.08) was found between OCs and RPSs generated using less restrictive thresholds.
Conclusions: RPS1 predicts case-control status only in the presence of serious OCs. Our data raise the possibility that the weak effect sizes of the GWAS SNPs is because they only increase risk in the context of developmental risk factors, which are not universal. Our results require replication in other samples.

Keywords: schizophrenia, obstetric complications, GWAS derived Risk Profile Scores, neurodevelopment, gene-environment interaction

SYMPOSIUM
Intergenerational Transmission of Psychiatric Risk

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Confederation 5/6 – Mezzanine
Chair: Alicia K. Smith*

***Supported by:** R01MH100122

11. Maternal Trauma and Psychopathology Predict Problematic Parenting

Dorthie Cross

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

Background: The impact of trauma and mental health on parenting behavior is an important mechanism of intergenerational risk.
Methods: We interviewed 135 largely low-income adult women who self-identified as African American using the Beck Depression Inventory-II, Modified PTSD Symptom Scale, Childhood Trauma Questionnaire, Traumatic Events Inventory, Child Abuse Potential Inventory, Parenting Scale, and Parenting Stress Index.
Results: We found that PTSD, depression, and child and adult trauma were significantly positively correlated with a range self-reported problematic parenting attitudes and behaviors, including child abuse potential, harsh reactivity, dysfunctional parent-child interactions, and general parental distress. In an ANOVA, maternal experience of child trauma (none, one type, or two or more types), F=6.06, p<.01, and maternal psychopathology (none, depression only, PTSD only, or both), F=14.12, p<.001, independently predicted child abuse potential such that experiencing multiple types of childhood trauma and having PTSD comorbid with depression each significantly predicted greater child abuse potential. In this analysis, depression alone was also a stronger predictor than PTSD alone. A bootstrap analysis examining whether PTSD and depression would mediate the effect of childhood trauma on child abuse potential yielded a significant direct effect of childhood trauma, 95% CI [.23, 1.67] and a significant indirect effect of depression, 95% CI [.71, 1.79], but not PTSD, 95% CI [-.30, .69].
Conclusions: Maternal trauma, depression, and PTSD are associated with serious problems in parenting. These problems may represent one mechanism, among many, of intergenerational traumatization and mental health risk.

Keywords: parenting, child abuse, intergenerational risk, depression, PTSD
Supported by: MH018264; MH071537

12. Psychophysiological Biomarkers of Anxiety in Children of Traumatized Mothers: Intergenerational Effects

Tanja Jovanovic[1], Dorthie Cross[1], YeJi Kim[1], Alexander Vance[1], Renuka Reddy[1], Bekh Bradley[1,2]

[1]Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, [2]Mental Health, Atlanta VAMC, Decatur, GA

Background: A growing number of studies indicate that low income, African American men and women living in urban environments are at high risk for trauma exposure, which may have intergenerational effects. Physiological responses such as startle response and heart rate can serve as biomarkers of anxiety in adults and children.
Methods: The current study employed psychophysiological methods to describe biomarkers of fear and anxiety in children of trauma exposed mothers. We recruited mothers and 8-to-12-year-old children from a low SES, highly traumatized urban population. Adult women were assessed for childhood and adult trauma exposure, symptoms of depression and posttraumatic stress disorder, as well as parenting behavior. In addition, we assessed startle responses in children and mothers using electromyographic recordings of the eyeblink muscle, and heart-rate variability during the startle experiment using electrocardiogram.
Results: We found that maternal childhood trauma was predictive of her child's startle responses ($p<0.05$) and heart-rate variability ($p<0.01$), even after controlling for the child's own trauma exposure and maternal psychopathology. Atypical maternal parenting behavior, such as a lack of warmth and anxious interactions with the child, also predicted child physiological response.
Conclusions: These results indicate that environmental and behavioral effects increase intergenerational risk for PTSD, as measured by psychophysiological markers of fear and anxiety in children. Such physiological responses are also observed in adults with PTSD and may serve as early biomarkers of risk in children. Intergenerational effects may be mediated by biological (genetic, epigenetic), or environmental (maternal parenting, shared trauma exposure) effects.

Keywords: Startle response, Heart rate variability, Anxiety, Parenting, Trauma
Supported by: R01MH100122; R01HD071982; NARSAD

13. Heritable Epigenetic Patterns of Stress-Responsive Genes in Traumatized Mothers and their Children

Alicia K. Smith

Psychiatry & Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

Background: Exposure to traumatic events increases psychopathology risk across the lifespan, potentially by influencing epigenetic patterns of specific genes. The goal of this study was to identify shared epigenetic patterns in a cohort of highly traumatized mothers and their children.
Methods: Saliva samples were collected from 65 mothers and their children from the Grady Trauma Project. Traumatic events were assessed with the TESI for children and the TEI for adults. The association between child and maternal DNA methylation was assessed for each CpG site (HumanMethylation450) using linear models that adjusted for the proportion of buccal cells in saliva, child sex and age.
Results: Methylation of 13,930 child CpG sites was predicted by methylation of their mothers (FDR<.05), 69% of which were attributable to sequence variation within 50 kilobases. The remaining 31% may be responsive to the environment and were enriched for synaptic transmission and receptor pathways (corrected p<.001). 1937 CpG sites associated with the number of traumatic experiences in both groups (p<.05). For example, methylation of a CpG site in neuregulin (NRG1) decreased with increasing number of traumatic exposures in children (p=.001) and their mothers (p=.004), and the same CpG site associated with NRG1 gene expression levels (p=.004) in the adults. Further examination of NRG1 revealed multiple CpG sites that were correlated between children and their mothers (FDR<.05).
Conclusions: This study suggests that intergenerational data can be particularly informative for understanding complex gene-environment relationships and suggests a potential mechanism through some genes that may be regulated in response to trauma.

Keywords: genetic, intergenerational, transgenerational, DNA methylation, trauma
Supported by: R01MH100122

14. Influence of Parental Olfactory Fear Conditioning on Offspring Biology

Brian Dias[1,2], Kerry Ressler[2,3]

[1]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, [2]Department of Psychiatry and Behavioral Sciences, Yerkes National Primate Research Center, Atlanta, GA, [3]Department of Psychiatry and Behavioral Sciences, HHMI-Emory University, Atlanta, GA

Background: Descendant generations bear imprints of ancestral experiences. In several instances of traumatic events, detrimental effects are accrued in the descendants, by way of neuropsychiatric outcomes. The contribution of social transmission vs biological inheritance to such outcomes is an important arena of research.
Methods: We trained F0 adult female mice (ancestral generation) to associate an odor (Acetophenone) with mild foot-shocks. This allowed us to ask how an environmental cue associated with an aversive outcome in the ancestral generation is perceived by the descendant generation . In addition, cross-fostering studies were carried out to dissect the contribution of maternal rearing environment to any effect
Results: Fear conditioning F0 female mice to Acetophenone caused subsequently conceived odor naïve F1 male offspring to display behavioral sensitivity to Acetophenone ($p = 0.025$, $t(27) = 2.23$). This effect persisted even after being reared by non-trained females ($p = 0.0011$, $F3,18 = 6.874$). Acetophenone is detected by the M71 odorant receptor and we find that the F1 generation have larger M71 glomeruli in the olfactory bulbs which cannot be reversed by cross-fostering {Dorsal M71 Glomerular Area: ($p < 0.0001$, $F(3,14) = 17.52$). Medial M71 Glomerular Area: ($p < 0.01$, $F(3,15) = 5.93$)}.
Conclusions: We conclude that ancestral maternal olfactory experience affects olfactory neuroanatomy and consequently behavior in the descendant generation via biological inheritance. This work allows us to appreciate how ancestral maternal trauma contributes

to the development of neuropsychiatric disorders such as phobias, and Post Traumatic Stress Disorder (PTSD) in a descendant generation.

Keywords: epigenetics, inheritance, transgenerational, maternal conditioning
Supported by: HHMI

SYMPOSIUM
Reducing Fear in Rodents: Implications for Fear and Anxiety Disorders

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Tudor 7 – Main Mezzanine
Chair: Sheena Josselyn*
Co-Chair: Paul Frankland

***Supported by:** CIHR

15. Synaptic Encoding of Fear Extinction

Vadim Bolshakov

Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA

Background: Increased activity of neurons in the medial prefrontal cortex (mPFC) contributes to encoding of fear extinction memory. As the amygdala, reciprocally connected with the mPFC, is also a component of fear extinction curcuitry, we explored the effects of fear extinction on synaptic mechanisms of mPFC-amygdala interactions.
Methods: In our studies, we achieved projection-specific activation of prefrontal inputs to different nuclei in the amygdala using optogenetic tools, and performing whole-cell recordings of photostimulation-induced synaptic responses in slices from fear-conditioned, extinguished and control mice.
Results: We found that synaptic strength was decreased in excitatory projections from the mPFC to the basolateral nucleus of the amygdala (BLA) following fear extinction, whereas inhibitory neurotransmission in the BLA was unaffected by behavioral training. Thus, the balance between excitation and inhibition in mPFC-BLA projections was shifted toward greater functional efficiency of inhibition. We found also that activation of mPFC projections to the BLA results in heterosynaptic inhibition of excitatory synaptic transmission in the auditory inputs to the amygdala, which deliver the conditioned stimulus information during recall of extinction memory, and this heterosynaptic inhibition is enhanced after extinction.
Conclusions: These synaptic plasticity mechanisms in the mPFC-amygdala circuits could contribute to the reduced expression of the conditioned fear response after training procedures leading to fear extinction.

Keywords: fear, memory, extinction, optogenetics, synapses
Supported by: R01MH090464

16. Hippocampal Neurogenesis and Forgetting

Paul Frankland

Neuroscience and Mental Health, Hospital for Sick Children, Toronto, ON, Canada

Background: New neurons are continuously added to the subgranular zone of the hippocampus throughout the lifespan, but the functional consequences of hippocampal neurogenesis remain unclear. While the majority of previous studies have examined the impact of increasing or decreasing hippocampal neurogenesis on subsequent memory formation, few have examined the effects of similar manipulations on established, hippocampus-dependent memories. Computational models predict that addition of new neurons should lead to extensive remodeling of hippocampal circuits, and consequently degradation or forgetting of established memories. Consistent with this, lifespan changes in hippocampal neurogenesis are inversely correlated with memory persistence: During infancy, when hippocampal neurogenesis levels are high, freshly-generated memories tend to be rapidly forgotten. In contrast, during adulthood, when neurogenesis levels are lower, memories are typically much more persistent.
Methods: We have conducted two types of experiments that suggest that neurogenesis and forgetting are causally related. In these experiments we used genetic, pharmacological and behavioral interventions to manipulate levels of hippocampal neurogenesis in mice and studied the impact of these manipulations on contextual fear memories.
Results: First, in adult mice (P60), we find that increasing neurogenesis after memory formation is sufficient to induce forgetting. Second, in infant mice (P17), we find that decreasing neurogenesis after memory formation mitigates normal forgetting observed at this age.
Conclusions: Our data suggest a causal relationship between neurogenesis and memory persistence, and provide a neurobiological account for infantile amnesia.

Keywords: neurogenesis, forgetting, hippocampus
Supported by: CIHR77561

17. Optogenetic Manipulations of Neuronal Ensembles for Memory

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Background: Neuronal ensembles play important roles in the formation and alternation of fear memories. We asked the questions whether and how we could control the memory by directly manipulating these neuronal ensembles.
Methods: To identify and control the neuronal ensembles for an engram underlying a particular memory, we combined optogenetics with an activity-dependent, doxycycline-regulatable system. Using channelrhodopsin-2, we labeled neurons active during contextual fear conditioning in areas such as the dentate gyrus of the hippocampus, and later selectively activated these cells with light.
Results: By activating dentate gyrus neurons that were active during contextual fear conditioning, we induced fear recall in a context different from the original context. By light-activating cells

encoding for a neutral context while presenting foot shock in a different context, we created false fear memories for the previously neutral context. We could also induce the recall of memories associated with either positive or negative valence, and even switch the emotional valance of a memory. Finally, repeated light activation of the neuronal ensembles for a memory could also weaken that memory.
Conclusions: This system grants us the ability to dissect and control memory, reveals the flexible and dynamic nature of memory, and thus greatly enhances our understanding for the fundamental mechanisms of learning and memory.

Keywords: memory, neuronal ensembles, optogenetics
Supported by: HHMI, RIKEN

18. The Dynamic Memory Trace: Mechanisms Underlying Retrieval-dependent Processes

Cristina Alberini

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Background: Memories become fragile after retrieval.
Methods: Studies from my lab have employed inhibitory avoidance (IA) in rats to identify the molecular mechanisms and circuitry underlying retrieval-dependent processes that contribute to memory persistence and storage.
Results: I will discuss recent findings showing the role of IA post-retrieval mechanisms that can lead to either disruption or enhancement of memory.
Conclusions: Memory storage is highly dynamic. Retrieval contributes to create a complex network of stored experiences, which is highly dynamic and modifies with the changing environment. I will discuss potential targets important for designing novel strategies that can either weaken pathogenic memories of memory components or, conversely, enhance strength and persistence of adaptive memories.

Keywords: Fear, Anxiety, Rodents
Supported by: NIMH

SYMPOSIUM
New Frontiers in Neuromodulation: Technologies, Techniques, and Translation

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Ontario – Convention Floor
Chair: Darin D. Dougherty*

***Supported by:** Defense Advanced Research Projects Agency

19. Closing the Loop for Deep Brain Stimulation: Examples from Emotion Regulation

Alik Sunil Widge

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Background: Deep brain stimulation (DBS) has made great strides in treating neurologic disorders. We have not achieved similar results in trials of DBS for psychiatric illness. Although initial results in depression were promising, randomized trials (RCTs) at two targets failed to meet their endpoints. All trials to date have been with static disorders whose symptoms change over weeks. A large yet unaddressed class of diseases, particularly the anxiety/trauma spectrum, have symptoms that flare and remit over minutes to hours.
Methods: One solution is “closed loop” DBS -- stimulators that sense the brain, then respond in with stimulation customized to the immediate need. The challenge is the lack of biomarkers. Hardware exists for closed-loop stimulation, but there is no known electrical signature for symptoms. I propose a biomarker-free approach, where the focus is on top-down regulation: the patient’s capacity to regulate his/her own symptoms.
Results: I will show results and videos from preliminary rodent tests of the system, where 100% of pilot animals were able to learn and effectively use a prototype closed-loop stimulator. I will then discuss results that have emerged in the fear/extinction literature over the past decade that show how this can be a viable approach for trauma-related disorders.
Conclusions: Closed-loop DBS based on principles and circuits of emotion regulation appears feasible, and the general stimulation regimes that should be trialed are known in the animal literature. I will present a path forward for pre-clinical testing of multiple approaches.

Keywords: Deep brain stimulation, neuromodulation, post-traumatic stress disorder, amygdala, prefrontal cortex
Supported by: NSF Center for Sensorimotor Neural Engineering ; Picower Institute for Learning & Memory

20. Rational Design of Non-Invasive Oscillatory Brain Stimulation

Flavio Frohlich

Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill

Background: Progress in research and development of novel brain stimulation paradigms has been hampered by the lack of understanding how stimulation parameters should be selected.
Methods: We combined EEG with cognitive testing and transcranial alternating current stimulation (tACS) to elucidate how endogenous cortical activity patterns shape the response to non-invasive oscillatory stimulation and how such changes in brain activity patterns modulate cognition. In particular, we aimed to test the hypothesis that task-specific oscillatory EEG patterns provide a rational basis for the design of stimulation paradigms to modulate and enhance cognition.
Results: We re will report the results of two studies that aimed at enhancing higher order cognitive functions with tACS. In the first study, we found that endogenous recruitment of gamma oscillations (30-50 Hz) significantly correlated with the behavioral modulation by 40Hz-tACS in a working memory task ($r=0.67$, $p=0.017$, $N=15$). Therefore, (1) tACS enables frequency-specific modulation of cortical dynamics and (2) individualization of stimulation is required for successful cognitive enhancement. In the second study, we used 10Hz-tACS to enhance alpha oscillations that are correlated with creative ideation based on EEG data. We found a significant increase in creativity in comparison to sham ($7.45\ \% \pm 3.11\ \%$, $p = 0.036$), demonstrating the importance of EEG biomarkers for the design of tACS paradigms.
Conclusions: Our results provide guidance for the rational design

of non-invasive brain stimulation paradigms for the treatment of cognitive impairment and psychiatric symptoms mediated by deficits in the cortical activity structure.

Keywords: transcranial alternating current stimulation, tACS, cognition, EEG
Supported by: R01 MH101547

21. Low-Intensity Focused Ultrasound as a Novel Method for Deep Non-Invasive Neuromodulation

William Jamie Tyler

School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ

Background: There is a need for improved tools capable of modulating deep-brain circuits. For research, diagnostics, and therapies it would be an added advantage if these tools were noninvasive. Over the past decade we have shown that pulsed ultrasound is capable of non-invasively modulating brain circuits.
Methods: We will first discuss the rationale behind the use of pulsed ultrasound for neuromodulation by describing its basic biophysical characteristics while providing indisputable evidence that it can be readily transmitted and focused through the human skull to deep-brain regions. We will then basic observations made in electrophysiological and imaging studies conducted in rodents, pigs, monkeys, and humans.
Results: Recent data demonstrating that transcranial focused ultrasound can modulate the amplitude and phase of intrinsic and evoked human EEG signals will be presented. We will then present unpublished observations demonstrating that transcranial focused ultrasound can modulate fMRI BOLD signals in non-human primates and humans. We will present cellular evidence describing the mechanisms of action underlying the ability of pulsed ultrasound to modulate brain activity without temperature increases. Finally we will describe our ongoing efforts to demonstrate transcranial focused ultrasound can be used as a non-invasive tool for probing limbic system structures.
Conclusions: The continued development of this capability will provide a platform for target verification in neuropsychiatric applications of conventional DBS, as well as lend itself to developing a new generation of robust therapeutic and diagnostic tools enabling the non-invasive modulation of deep-brain structures.

Keywords: ultrasound, deep-brain stimulation, EEG, fMRI
Supported by: McKnight Endowment for Neuroscience, DARPA, U.S. Army, and Thync, Inc.

22. Dissecting Neural Circuits in Preclinical Models to Inform OCD Neuromodulation Strategies

Susanne E. Ahmari

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Background: Deep brain stimulation (DBS) in ventral capsule/ventral striatum (VC/VS) shows great promise in some Obsessive Compulsive Disorder (OCD) patients; however, effects are only maintained via constant stimulation. Stimulation of particular cell subtypes using optogenetics could potentially lead to more lasting effects via plasticity changes.
Methods: Mice were injected with AAV-channelrhodopsin-EYFP in orbitofrontal cortex (OFC), and implanted with fiberoptics or stereo-optrodes in ventromedial striatum (VMS). Behavior (grooming, anxiety-like behavior, reversal learning) and firing rates were examined before, during, and after stimulation [473nm, 1-5mW, 10Hz, 10msec pulse width]. Data were analyzed using repeated-measures ANOVAs and post-hoc tests ($\alpha = 0.05$).
Results: Repeated OFC-VMS hyperactivation over multiple days generated a progressive increase in grooming ($p<.02$) that was sustained up to 2 weeks after stimulation ($p<.03$). In vivo recordings demonstrated temporal coupling of behavioral plasticity and OFC-VMS circuit plasticity ($p<.001$). Preliminary studies show further evidence for electrophysiologic and behavioral plasticity- i.e. sustained decreases in striatal theta power and impaired reversal learning. Ongoing experiments are testing whether OFC-VMS stimulation leads to plasticity and symptom reversal in transgenic OCD model systems.
Conclusions: Brief but repeated optogenetic stimulation of specific OFC-VMS projections leads to perseverative grooming and pathologic plasticity. We are now investigating whether cell-type-specific plasticity mechanisms can be harnessed to normalize pathologic behaviors and network activity in transgenic OCD mouse models. Unpublished and new data includes reversal learning data, in vivo electrophysiology demonstrating alterations in striatal theta power, and preliminary findings from optogenetic stimulation in transgenic OCD animal models.

Keywords: Obsessive Compulsive Disorder, OCD, optogenetics, plasticity, Deep Brain Stimulation
Supported by: NIMH K08MH087718; NIMH R01MH104255; Burroughs Wellcome CAMS Award; MQ Fellows Award; NARSAD Young Investigator Award

SYMPOSIUM
Infection and Immune Activation in Schizophrenia and Other Neuropsychiatric Disorders

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Confederation 3 – Mezzanine
Chair: Alan S. Brown*

***Supported by:** NIMH

23. Maternal Immune Activation Selectively Alters the Functioning of Parvalbumin Interneurons in the Offspring Prefrontal Cortex

Christoph Kellendonk

Psychiatry, Columbia University, New York, NY

Background: Alterations in the expression of GABAergic markers in the prefrontal cortex (PFC) have been observed in mental disorders such as schizophrenia, autism and depression. Specifically, decreased functioning of parvalbumin-expressing (PV) interneurons is thought to contribute to working memory deficits observed in schizophrenia. Well-established animal models of environmental risk factors, such as maternal immune activation (MIA) during prenatal development, recapitulate the histological abnormalities in prefrontal interneurons found in patients. It is unclear, however, whether the histological changes reflect physiological changes in interneuron function and whether the potential functional changes are selective to PV interneurons.
Methods: To address this question we measured functional connectivity between genetically defined interneuron populations and excitatory projection neurons in the PFC of adult MIA offspring

using optogenetic tools combined with patch-clamp slice-physiology. We further analyzed the behavior of MIA treated offspring.
Results: We found that MIA leads to a deficit in the ability of PV interneurons to inhibit PN neurons in the PFC without affecting the function of another major class of interneurons that expresses calretinin (n=26/37, p<0.001). Surprisingly, despite a profound impairment in PV to PN connectivity, MIA offspring showed no deficits in working memory but displayed increased anxiety-related behaviors (n=18/15, p<0.01).
Conclusions: Maternal immune activation leads to specific changes in the functioning of prefrontal PV interneurons in the offspring, suggesting that PV interneurons are particularly vulnerable to this developmental impact. These functional changes are associated with increased anxiety, emphasizing a role of these neurons in mood dysregulation rather than working memory.

Keywords: maternal immune response, parvalbumin interneurons, prefrontal cortex, electrophysiology, working memory
Supported by: Sackler Institute, NARSAD

24. Transgenerational Transmission and Modification of Behavioral Deficits Induced by Prenatal Immune Activation

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Background: Environmentally acquired brain dysfunctions can be transmitted to offspring across multiple generations, presumably via epigenetic modifications. Here, we explored whether such transgenerational effects can be induced by an established environmental risk factor of developmental neuropsychiatric disease, namely prenatal infection.
Methods: Pregnant mice (F0) were injected with the viral mimetic poly(I:C) (5 mg/kg) or control solution on gestation day 9. To examine whether behavioral deficits in direct descendants (F1) can be transmitted to subsequent generations, we generated F2 and F3 offspring by inter-crossing F1 or F2 offspring, respectively. In addition, we performed epigenetic analyses exploring the methylation patterns of promoter regions of enzymes that regulate GABA biosynthesis (GAD65 and GAD67).
Results: Deficits in social interaction (p<0.01), short-term memory (p<0.05) and cued fear conditioning (p<0.01), all of which emerge in the F1 offspring, are also present in the F2 and F3 generation. Intriguingly, F2 and F3 offspring further developed abnormalities in depression-like behavior, which in turn were not present in the direct F1 descendants born to immune-challenged mothers. We further found enhanced methylation and hydroxymethylation levels at the GAD65 (p<0.05) and GAD67 (p<0.05) promoters, which were concomitant to reduced mRNA expression of these two genes in prefrontal cortex of the F1 offspring.
Conclusions: Our novel and unpublished findings demonstrate that behavioral deficits induced by prenatal infection can be transmitted and modified across subsequent generations. The presence of hypermethylated promoter regions of GABAergic markers in the F1 offspring provides a first indication for the involvement of epigenetic mechanisms in this association.

Keywords: Autism, Epigenetics, Immune System, Maternal Infection, Schizophrenia
Supported by: SNSF_310030_146217/1;FP7/2007–2011_259679

25. Elevated Maternal C-reactive Protein and Increased Risk of Schizophrenia in a National Birth Cohort

Alan Brown[1], Sarah Canetta[2], Andre Sourander[3], Heljä-marja Surcel[4], Susanna Hinkka-Yli-Salomäki[3], Jaana Leiviskä[5], Christoph Kellendonk[6], Ian McKeague[7]

[1]Department of Psychiatry, Columbia University, New York, NY, [2]Division of Molecular Therapeutics, Columbia University, New York, NY, [3]Department of Child Psychiatry, University of Turku, Turku, Finland, [4]Department of Children, Young People and Families, National Institute of Health and Welfare, Oulu, Finland, [5]Departmetn of Chronic Disease Prevention, National Institute of Health and Welfare, Oulu, Finland, [6]Department of Pharmacology, Columbia University, New York, NY, [7]Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY

Background: Mounting epidemiological and preclinical evidence implicates prenatal infection and subsequent immune activation in the etiology of schizophrenia. Inflammation during pregnancy may represent a common pathway by which different infections increase risk for the disorder. The goal of the present study was to evaluate whether maternal, prospectively assayed early to mid-gestational C-reactive protein (CRP), an established inflammatory biomarker, is associated with schizophrenia in a large national birth cohort with an extensive serum biobank.
Methods: This study utilized a nested case-control design from the Finnish Prenatal Study of Schizophrenia birth cohort. 777 schizophrenia cases (630 with schizophrenia, 147 with schizoaffective disorder) that had maternal sera available for CRP testing were identified from this cohort and matched to 777 controls in the analysis. Maternal CRP levels were assessed using a latex immunoassay from archived maternal serum specimens.
Results: Increasing maternal CRP levels were significantly associated with schizophrenia in offspring (adjusted odds ratio (OR)=1.31, 95% confidence interval (CI)=1.10-1.56, p=0.003). Separate analysis by sex revealed a significant association in males (OR=1.18, 95% CI=1.02-1.38, p=0.029) but not in females (OR=1.11, 95% CI=0.91-1.38, p=0.29). The association was greater among cases born post-term (p=0.05).
Conclusions: This finding provides novel evidence to date that maternal inflammation may play a significant role in schizophrenia. Unpublished data indicate a significant association between maternal CRP and schizophrenia in males but not in females, and a greater effect among cases born post-term. These findings have implications for identifying preventive strategies and pathogenic mechanisms in schizophrenia and other neurodevelopmental disorders.

Keywords: C-reactive protein, Maternal, Epidemiology, Schizophrenia, Immune
Supported by: 5R01MH082052

26. The Virome of Individuals with Schizophrenia

Robert Yolken

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Background: Mucosal sites such as the oropharynx contain a wide range of microorganisms, collectively designated as the microbiome. The microbiome can affect behavior through a number of neurobiological and immunological mechanisms relevant to the pathogenesis of schizophrenia.
Methods: We employed metagenomic analysis to characterize bacteriophage genomes in the oral pharynx of 41 individuals with schizophrenia and 33 control individuals. This analysis was performed by the generation of more than 100,000,000 sequence reads from each sample and the mapping of these reads to databases.
Results: We identified 79 distinct bacteriophage sequences in the oropharyngeal samples. Of these, one bacteriophage genome, Lactobacillus phage phiadh, was found to be significantly different in individuals with schizophrenia ($p<0.00037$, $q<0.03$ adjusted for multiple comparisons). The differential levels of Lactobacillus phage phiadh remained significant when controlling for age, gender, race, socioeconomic status, or cigarette smoking (coefficient=2.0, $p<0.006$) and were correlated with the level of host bacterial DNA. Within the group of individuals with schizophrenia, the level of Lactobacillus phage phiadh was correlated with the prevalence of immunological disorders as well as with the administration of valproate, which has been shown in animal models to alter the microbiome.We have also found other novel viruses in the samples including ones previously thought to infect plants and algae.
Conclusions: The viral composition of the oropharynx in individuals with schizophrenia differs from that of controls and may be related to co-morbid immunological abnormalities

Keywords: Microbiome, Schizophrenia, Infection
Supported by: Stanley Medical Research Institute; NIMH

SYMPOSIUM
Neuroimaging Strategies to Predict Response in Treatment Studies

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Alberta – Mezzanine
Chair: Aristotle Voineskos*

***Supported by:** R01MH099167 and Canadian Institutes of Health Research

27. Brain Activation Changes in Psychotic Disorders in Response to Targeted Cognitive Training

Dost Ongur, Kathryn Eve Lewandowski

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Background: Cognitive deficits are common in psychotic disorders such as schizophrenia and psychotic bipolar disorder and cognitive performance is the strongest predictor of community functioning. Treatments that improve cognitive function may significantly ameliorate quality of life and public health burdens. Evidence suggests that targeted cognitive training (TCT), which relies on repeated, appropriately reinforced cognitive exercises, may accomplish this task. However, not all patients respond to TCT; therefore markers of treatment response are needed to tailor therapeutic approaches.
Methods: In an ongoing study of a 6 month course of TCT, we have recruited 60 patients with bipolar disorder with psychotic features. Study is ongoing, however we have collected MRI data at baseline and following TCT completion in 18 patients randomized to TCT (N=10) or an active control condition (internet based quiz games). MRI data collected at 3T consist of structural, DTI, and resting state fMRI sequences as well as a Stroop-like multisource interference task (MSIT – not part of TCT) fMRI run.
Results: TCT improved cognitive function in a wide range of cognitive domains. Patients who received TCT showed greater activation in anterior cingulate cortex during MSIT than the control group. Greater cognitive improvement was associated with better community functioning 6 months after study completion.
Conclusions: TCT is an effective intervention in patients with psychotic bipolar disorder. Brain mechanisms of positive response to TCT involve enhanced focal neuronal activation during cognitive tasks. This is true even if the task was not part of TCT, suggesting a generalized mechanism.

Keywords: cognitive remediation, anterior cingulate cortex, bipolar disorder, fMRI, MSIT
Supported by: R01MH094594; K23MH091210

28. Antipsychotic Treatment and Functional Connectivity of the Striatum: A Prospective Controlled Study in First-Episode Schizophrenia

Anil Malhotra

Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY

Background: Previous evidence has implicated corticostriatal abnormalities in the pathophysiology of psychosis. Although the striatum is the primary target of all efficacious antipsychotics, the relationship between its functional connectivity and symptomatic reduction remains unknown.
Methods: We examined the longitudinal effects of treatment with second-generation antipsychotics on functional connectivity of the striatum during resting state MRI in 24 first-episode psychosis patients and 24 matched controls. Patients were scanned at baseline and after 12 weeks of controlled treatment with either risperidone or aripiprazole. Psychotic symptoms were evaluated with the BPRS at baseline and follow-up. Healthy participants were scanned twice with a twelve week interval to account for the effects of time and/or habituation to the scanning environment. Functional connectivity of striatal regions was examined using a seed-based approach with a GE 3T magnet.
Results: As psychosis improved, we observed an increase in functional connectivity between striatal seed regions and the anterior cingulate, dorsolateral prefrontal cortex, and limbic regions including the hippocampus and anterior insula. Conversely, a negative relationship was observed between reductions in psychosis and connectivity of striatal regions with structures within the parietal lobe. In a follow-up analysis, baseline connectivity measures predicted antipsychotic response in a larger cohort of 41 first episode subjects; a result which replicated in an independent cohort of 40 chronic patients with psychosis.

Conclusions: Increased functional connectivity of the striatum with prefrontal and limbic regions may be a biomarker for improvement in symptoms associated with treatment, and may also provide a predictive assay for antipsychotic drug response.

Keywords: connectivity, psychosis, striatum, antipsychotic, biomarkers
Supported by: NIMH

29. The Neurobiology of Treatment Resistance: Window into the Heterogeneity of Schizophrenia

Adrienne C. Lahti

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Background: Approximately 30% of patients with schizophrenia (SZ) will not improve with antipsychotic drug (APD) treatment. In this study, we hypothesized that pretreatment brain functional connectivity (FC) and neurochemistry would be predictive of treatment response. We measured the FC of the ventral tegmental area (VTA) and obtained glutamate + glutamine (Glx) levels in the dorsal anterior cingulate cortex (dACC) prior to treatment.
Methods: Unmedicated SZ (n=21) were first scanned and then entered into a 6-week APD trial. Resting state scans were acquired during a 5-min gradient recalled EPI sequence. Using a seed-based approach, we examined the FC of the VTA. Using MR Spectroscopy (PRESS; TR/TE = 2000/80 msec), we collected data from a voxel in the dACC (2.7 x 2 x 1 cm^3).
Results: Pre-treatment VTA connectivity strength to the dACC was positively correlated with good response to a 6-week course of APD, whereas connectivity to the default mode network (ventromedial prefrontal, posterior cingulate, precuneus) was negatively correlated (FDR corrected at <0.05). Pre-treatment dACC Glx levels were positively correlated (r (18) = .48, p = .03) with subsequent good response.
Conclusions: VTA FC in unmedicated patients predicted patients' subsequent response to treatment, suggesting that the brain is wired in a way that does or does not favor treatment response. In addition, pretreatment
ACC Glx might index the potential for brain's plasticity in response to treatment. These results suggest that patients who do not respond to medication have an underlying neurobiology that is different than those who do.

Keywords: schizophrenia, treatment response, functional connectivity, MR Spectroscopy, ventral tegmental area
Supported by: R01MH081014

30. Resting-State Functional Neuroimaging, Treatment Mechanisms, and Response in Intervention Studies

Aristotle Voineskos[1], Nicholas Neufeld[1], Colin Hawco[1], Alastair Flint[2], Jeff Daskalakis[1], Benoit Mulsant[1]

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Background: The use of neuroimaging in clinical trials can provide mechanisms of treatment efficacy and predict response. Resting-state fMRI is a flexible, easy-to-implement technique in clinical trials. The objective of this presentation is to demonstrate in two different intervention studies how brain network connectivity during the resting-state can be used at baseline.
Methods: In the first study, patients with remitted psychotic depression received a baseline neuroimaging scan prior to randomization to continuation vs. discontinuation of antipsychotic treatment. Default mode network (DMN) connectivity from the baseline resting-state condition fMRI scan was compared in these patients (n=21) to a matched control group (n=21). In the second study, patients with schizophrenia received a baseline neuroimaging scan prior to randomization to active vs. sham rTMS applied to bilateral DLPFC to improve working memory performance. Fronto-parietal network connectivity from the resting-state fMRI scan was compared between patients and controls at baseline.
Results: When compared with controls, patients with remitted psychotic depression showed statistically significant (P<0.05, corrected) decreased connectivity between the DMN and bilateral insular cortex. When compared with controls, schizophrenia patients had increased connectivity between the left and right fronto-parietal networks and cerebellum.
Conclusions: These functional brain alterations serve as key 'starting points' at the outset of treatment trials since they may serve as biomarkers across the duration of the trial. Differences among patient groups in these networks across the duration of the trial can then be interpreted as mechanisms of treatment efficacy, and baseline scans may offer predictive value for determining response.

Keywords: MRI, antipsychotics, TMS, treatment response
Supported by: R01MH099167; CIHR

SYMPOSIUM
Neural and Genetic Basis of Childhood Irritability: Implications for Neurobiologically-Informed Treatment

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Library – Mezzanine
Chair: Ellen Leibenluft*
Co-Chair: Wan-Ling Tseng

***Supported by:** NIMH Intramural Research Program

31. Neural Correlates of Irritability across Diagnoses: Categorical and Dimensional Approaches

Wan-Ling Tseng[1], Melissa A. Brotman[1], Christen M. Deveney[2], Elizabeth Moroney[1], Laura Machlin[1], Kenneth Towbin[1], Daniel S. Pine[1], Ellen Leibenluft[1]

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Background: Irritability is a core feature of disruptive mood dysregulation disorder (DMDD), yet it cuts across many other pediatric disorders, making it suitable to be studied under the Research Domain Criteria (RDoC) framework. We utilized a frustrating fMRI task to examine the neural correlates of irritability using two complementary approaches. First, we examined associations between brain activation and a dimensional measure of irritability. Next, we employed a categorical approach to compare activation across four diagnostic groups: DMDD, attention-deficit/hyperactivity disorder (ADHD), anxiety disorder (ANX), and healthy volunteers (HV).
Methods: 19 DMDD, 16 ADHD, 24 ANX, and 31 HV youths (mean age=12.8 years; 53.3% girls) completed an affective Posner task

while fMRI data **were** acquired. Frustration was elicited by providing participants rigged feedback. Parent report of the Affective Reactivity Index scale was used as a dimensional measure of irritability.
Results: Groups differed on parent-reported irritability (p<.001;D-MDD>ADHD=ANX>HV). Dimensional analyses revealed that higher irritability was related to decreased activation in parahippocampal gyrus during positive (r=-.24, p=.02) but not rigged feedback (r=.08, p=.46). Whole-brain 4(Group: DMDD, ADHD, ANX, HV)×2(Condition: Rigged vs. Positive Feedback) ANOVAs revealed within-group differences only in DMDD in superior temporal gyrus and parahippocampal gyrus. Generally consistent with the dimensional findings, DMDD youth showed increased activation in these regions when receiving rigged vs. positive feedback (ps≤.003).
Conclusions: Preliminary findings in this first fMRI study on DMDD suggest that abnormal neural activation in the parahippocampal gyrus and superior temporal gyrus, regions implicated in emotion regulation and social perception, may mediate irritability in youth.

Keywords: irritability, DMDD, fMRI, categorical, dimensional
Supported by: This research was supported by the Intramural Research Program of the NIMH.

32. Genetic and Environmental Contributions to the Expression of Irritable Mood and Behavior

Roxann Roberson-Nay

Psychiatry, Virginia Commonwealth University, Richmond, VA

Background: Little is known about genetic and environmental contributions to pediatric irritability.
Methods: Twin children (9-13 years) completed the Affective Reactivity Index (ARI), which assesses symptoms of pediatric irritability, during a laboratory visit where juvenile twins also completed the Modified Affective Posner (MAP), a cognitive-neuroscience task that elicits frustration and irritability. A parent also completed an ARI about each of their twin children. We will present outcomes associated with the ACE model, which allows for the disaggregation of variance into additive genetic (A), shared (common) environment (C), and unique (nonshared) environment (E) contributions using data from monozygotic (MZ; share 100% of segregating alleles) and dizygotic (DZ; share ~50% of segregating alleles) twins. Data collection is ongoing.
Results: Preliminary estimates (n=128 pairs) of genetic and environmental influences were estimated using MZ and DZ twin-twin correlations. For the self and parent completed ARI, estimates indicated that the MZ twin correlation was almost twice that of the DZ correlation, suggesting genetic influences. A preliminary examination of the pairwise concordance rate for the MAP also suggested that MZ twins were more highly correlated for overall frustration levels and valence ratings compared to DZ twins, again suggesting that genes play a significant role in the behavioral expression of irritability. As a next step, we will conduct a bivariate analysis of the ARI and MAP to determine shared genetic and environmental covariation.
Conclusions: These data will inform discussion of the contribution of genes versus environmental factors to irritable mood and its behavioral manifestation.

Keywords: irritability, mood, behavioral, twins, genetic
Supported by: R01MH101518

33. Methylphenidate Treatment of Chronic Irritability: Symptom Improvement and Underlying Neural Mechanisms

Leslie Hulvershorn

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Background: Some children with ADHD display chronic irritability with temper outbursts. Despite high rates of medication use, little is known about effective pharmacotherapies for the mood regulation component of their symptoms. Methylphenidate (MPH) is a dopamine and norepinephrine acting agent with known benefit for multiple symptoms of ADHD, including emotion regulation. Neural mechanisms underlying MPH's effects on emotion aren't well characterized.
Methods: Medication-free, right-handed 10-15 year olds (n=23) with ADHD and disruptive mood dysregulation disorder were treated open-label with MPH (Concerta ™). Functional MRI scans using a facial emotion-matching task were acquired *before and after 4 weeks of MPH treatment*. A whole brain voxel-wise analysis (p<0.05) compared face – shape activation from pre- to post-medication scan.
Results: All participants tolerated dose escalation with few side effects. A significant improvement on parent ratings of the Emotion Regulation Checklist was noted from baseline to week 4 of treatment (p=0.01). On the task, participants demonstrated similarly high rates of accuracy when matching shapes (>90%) and faces (>70%). There were no differences between pre- or post-scans for face or shape matching accuracy. Significant pre- vs. post-medication BOLD signal activation increases in the right inferior frontal gyrus (k=62 voxels) and right cerebellum (k=105) were found.
Conclusions: In this unpublished, open-label fMRI study, MPH was well tolerated at therapeutic doses and resulted in parent-rated improvements in emotion regulation. MPH appears to have increased BOLD activation in the inferior frontal gyrus, a region associated with inhibitory control, suggesting influences of cognitive control regions on emotion regulation.

Keywords: methylphenidate, irritability, attention deficit hyperactivity disorder, disruptive mood dysregulation disorder
Supported by: Brain and Behavior Research Foundation; Klingenstein Third Generation Foundation; IU Health

34. Cognitive Remediation for Cognitive Flexibility in Bipolar Youths: Preliminary Findings

Daniel P. Dickstein

Dept Psychiatry & Human Behavior, Bradley Hospital / Brown University, East Providence, RI

Background: From a neuroscience perspective, irritability may result from impaired cognitive flexibility_meaning the ability to adapt to changing rewards and punishments. From a clinical perspective, bipolar disorder (BD) is one of several psychiatric disorders affecting children invo;vling irritability and impaired cognitive flexibility for which there is a pressing need for novel, brain-based treatments. To address this need, we conducted a pilot study of computer-assisted cognitive remediation for cognitive flexibility in pediatric BD. We assessed the feasibility, acceptability, and potential engagement of brain and behavior targets underlying reversal learning.

Methods: We conducted a stage 1a trial of computer-assisted cognitive remediation for cognitive flexibility in BD youths. This study was IRB-approved and conducted at Bradley Hospital and Brown University. Brain target outcome variable was prefrontal cortex (PFC)-amygdala-striatal engagement during reversal learning errors. Behavioral target outcome was simple reversal learning errors from the Cambridge Neuropsychological Automated Testing Battery (CANTAB) Intra-dimensional/extra-dimensional (IDED) set-shifting task.
Results: Our team of collaborators developed a web-based computer assisted cognitive remediation that was delivered in our laboratory to our target of 12 BD youths. By parent and participant ratings, this was viewed as acceptable. Preliminary event-related functional magnetic resonance imaging results suggest that we did engage PFC during reversal errors.
Conclusions: Our data suggests that computer-assisted cognitive remediation for cognitive flexibility is feasible, acceptable, and may engage the brain/behavior mechanisms underlying reversal learning. Further work is required to determine if this is due to our cognitive remediation or is a non-specific effect of coming into our lab.

Keywords: bipolar disorder, child, cognition, treatment, neuroimaging
Supported by: 5R21MH096850

SYMPOSIUM
Translational Studies of Motivational Deficits

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
British Columbia – Mezzanine
Chair: Gabriel S. Dichter
Co-Chair: Michael T. Treadway*

***Supported by:** R21 MH094781

35. Not All Antidepressants are Created Equal: Differentiating Drugs Based Upon Their Effort-related Motivational Effects in Animal Models

John D. Salamone[1], Samantha Yohn[1], Merce Correa[2]

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Background: Tests of effort-based decision making in rodents are being developed as models for motivational symptoms such as anergia/fatigue, which are seen in people with depression and other disorders. Effort-related decision making is studied by offering a choice between a highly valued reinforcer that requires higher effort to obtain vs. a low reward/low effort option.
Methods: Conditions associated with motivational symptoms (stress, proinflammatory cytokines, dopamine (DA) depletion) affect effort-related decision making in rats, causing animals to shift their choices away from tasks with high effort requirements, and instead select less effortful activities. These effects are not due to motor incapacitation, "anhedonia", or changes in appetite or food preference. Tetrabenazine, a VMAT-2 inhibitor that blocks DA storage, induces depressive symptoms in humans. In rats, administration of tetrabenazine at doses that reduce accumbens DA transmission alters effort-related decision making, biasing animals towards low-effort alternatives.
Results: These effects can be reversed by coadministration of the catecholamine uptake blocker bupropion, an affect that depends upon stimulation of DA receptors. Moreover, the selective DA uptake blocker GBR 12909 fully reverses the effort-related effects of tetrabenazine. In contrast, the norepinephrine uptake blocker desipramine and the 5-HT uptake blocker fluoxetine fail to reverse the effects of tetrabenazine, and actually suppress lever pressing.
Conclusions: These studies are consistent with the human literature indicating the involvement of DA in motivational symptoms, and the relative lack of effect of 5-HT uptake blockers on anergia/fatigue in humans. Moreover, they suggest that potential therapeutic agents can be differentiated based upon their effort-related effects in animal models.

Keywords: dopamine, fluoxetine, motivation, anergia fatigue, serotonin
Supported by: NIMH, University of Connecitut Research Foundation

36. Mesocorticolimbic Predictors of Responses to Psychotherapy in Major Depression

Gabriel S. Dichter[1], Moria Smoski[2], Andrew Crowther[3], Jared Minkel[2], Tyler Moore[2], Devin Gibbs[1], Chris Petty[4], Josh Bizzell[1], Crystal Elder Schiller[1], John Sideris[5], Hannah Carl[6]

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Background: Anhedonia is a core feature of major depressive disorder (MDD) and previous research has implicated hypoactivation in mesolimbic structures in the pathophysiology of this symptom domain. However, linkages between anhedonia, mesolimbic brain function, and response to antidepressant treatment are not well understood.
Methods: Across three interrelated studies, we investigated relations between mesolimbic brain activation and connectivity, anhedonia, and response to behavioral activation (BA) psychotherapy, a treatment specifically designed to increase approach-oriented behaviors towards goals, in MDD.
Results: Across all studies, we found that approximately 75% of outpatients with MDD were treatment responders. In the first study, we found that BA psychotherapy caused changes in neural response to rewards in a number of mesolimbic regions, including the caudate nucleus during reward anticipation and the orbital frontal cortex during receipt of rewards. In the second study, we found that the persistence of caudate nucleus activation during reward anticipation predicted response to BA psychotherapy. In the third study, hierarchical linear modeling revealed that improvements in anhedonic symptoms in response to BA psychotherapy were predicted by pretreatment resting state connectivity between the right insula and the right middle temporal gyrus predicted response to BA psychotherapy.
Conclusions: These studies highlight the critical role that mesolimbic reward processing brain regions play in terms of under-

standing potential mechanisms of action of BA psychotherapy as well as predicting response to BA psychotherapy. Future research will evaluate the capacity of these metrics to predict response to different antidepressant modalities to inform treatment decisions for patients with MDD.

Keywords: depression, fMRI, resting state, psychotherapy, treatment outcomes
Supported by: R21 MH094781

37. Neural Mechanisms of Effort-based Decision-making in Psychopathology

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Background: Psychiatric symptoms related to fatigue, anhedonia and low-motivation are common across many disorders. Previously, we have shown that such symptoms may reflect impairments in the ability to allocate effort resources effectively during goal-directed behavior. Preclinical studies suggest that this deficit may result from alterations in a valuation circuit comprised of ventromedial prefrontal cortex (vmPFC) and the ventral striatum, but empirical evidence is lacking.
Methods: Here, we present data from a recent functional neuroimaging study of 42 outpatient depressed patients and demographically-matched controls who were scanned while making a series of decisions regarding effort allocation using a novel effort-based decision-making paradigm. A parabolic discounting model was fitted to each subject to determine the trial-wise subjective value of different effort/reward combinations.
Results: Behaviorally, controls show significant greater sensitivity to the magnitude of rewards available when making effort-expenditure decisions, as compared to depressed patients. Across all subjects, trial-wise subjective value of different effort/reward combinations was shown to selectively elicit activity in vmPFC ($p < 0.05$, FDR corrected). However, sensitivity to reward magnitude was associated with great activity in the ventral striatum ($p < 0.05$, FDR corrected). Moreover, functional connectivity analysis using PPI revealed that sensitivity to reward magnitude was associated with greater vmPFC-striatal connectivity.
Conclusions: These results replicate and extend prior research suggesting the depressed patients are less responsive to available rewards when making effort-based decisions, and provide evidence for a functional disconnection between medial prefrontal valuation systems and the striatum as a potential mechanisms underlying this deficit.

Keywords: Depression, Effort-based Decision-making, ventromedial prefrontal cortex, striatum, fMRI
Supported by: NIMH R21MH092751; NIMH K99102355

38. Cytokines and Anhedonia: Subcortical Sources of Inflammatory Malaise

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Background: Inflammatory cytokines have been shown to alter basal ganglia activity including reward responsivity that may be mediated by cytokine effects on dopamine. We therefore endeavored to determine whether chronic administration of the inflammatory cytokine interferon (IFN)-alpha reduces ventral striatal responses to reward in humans and whether such changes were associated with decreased presynaptic striatal dopamine function and anhedonia. We also directly examined dopamine release in non-human primates following chronic IFN-alpha and correlated changes with effort-based reward behavior.
Methods: Neural activity in ventral striatum during a hedonic reward (gambling) task was measured by functional magnetic resonance imaging in 14 IFN-alpha-treated subjects and 14 controls, and uptake and turnover of radiolabeled [18F]DOPA in ventral striatum was assessed in 12 subjects prior to and after 4 weeks of IFN-alpha using positron emission tomography. Dopamine release in caudate was assessed in 4 rhesus monkeys after 4 weeks of saline or IFN-alpha using in vivo microdialysis.
Results: IFN-alpha was associated with decreased neural activity in ventral striatum that was associated with increased [18F]DOPA uptake and decreased [18F]DOPA release, both of which were associated with anhedonia. IFN-alpha was also associated with decreased extracellular dopamine release in non-human primates which correlated with decreased performance on an effort-based reward task. Administration of levodopa via reverse microdialysis reversed decreased dopamine release.
Conclusions: These data indicate that inflammatory cytokines such as IFN-alpha decrease ventral striatal activity and reduce hedonic reward in association with changes in presynaptic striatal dopamine function consistent with decreased dopamine synthesis and ultimately release.

Keywords: Inflammation, Cytokines, Dopamine, Reward, Neuroimaging
Supported by: National Institute of Mental Health

SYMPOSIUM
Prenatal Stress and Effects on the Child: Gene Environment Interactions and Epigenetic Associations with Intervention
Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Quebec – Mezzanine
Chair: Vivette Glover*

***Supported by:** NIH

39. Prenatal Anxiety and Child Emotional, Behavioural and Cognitive Outcomes; Gene Environment Interactions

Vivette Glover

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Background: If a mother is anxious or depressed during pregnancy her child is more likely to have emotional, behavioural or cognitive problems, even after allowing for a range of confounders. However most children are not affected, and those that are can be affected in different ways. Here we have tested the hypotheses that the effects of prenatal anxiety on child internalizing symptoms are moderated by genetic variation in the child's brain-derived neurotrophic factor (BDNF), and ADHD and cognitive symptoms by catechol-O-methyl transferase (COMT) genes
Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALPSPAC) population cohort (n=8584). Maternal anxiety was assessed by the Crown Crisp questionnaire at 32 weeks. Internalizing symptoms, and ADHD symptoms were assessed from 4 to 13 years of age using the Strengths and Difficulties Questionnaire, and ADHD diagnosis by the Development and Wellbeing Assessment (DAWBA) at 15 years. Working memory was assessed at age 8 by the backward digit span test. Obstetric and psychosocial risk and postnatal maternal symptoms were included as covariates.
Results: There was genetic moderation of the prenatal anxiety effect on internalizing symptoms by the BDNF polymorphisms (rs11030121 and rs7124442) up to age 13 ($p=0.018$ and $p=0.029$ respectively). COMT (val158met (rs4680)) genotype moderated the association between maternal prenatal anxiety and child ADHD in both childhood and adolescence ($p<0.05$), as well as working memory ($p<0.01$).
Conclusions: These new findings suggest a role for both BDNF and COMT gene/environment interactions in specific individual vulnerabilities to the effects of prenatal anxiety.

Keywords: Prenatal, anxiety, ADHD, working memory, genetics
Supported by: NIH grant R01 MH073842.

40. Fetal Behavior: Opposite Effects of Maternal Distress and SRI Use for Offspring with Risk Allele for the Serotonin Transporter Gene

Hanna C. Gustafsson[1], Leigh Cooper[2], Bettina Knight[3], D. Jeffrey Newport[4], Zachary N. Stowe[3], Catherine Monk[1]

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Background: Psychiatric symptoms and SRI use during pregnancy are associated with at-risk profiles in children's neurobehavioral development. Other data suggest allelic variation of the serotonin transporter genotype is associated with psychopathology. Despite the prenatal timing of the exposures, the clinical relevance of the co-occurrence of maternal mood, medication use, and the possible moderating role of the SERT genotype, no studies have considered together these influences in relation to fetal development.
Methods: In a prospectively followed sample of pregnant women with psychiatric histories (N=58), current symptoms ("distress") and psychotropic medication use were examined at 4-6 week intervals in relation to fetal heart rate (FHR), heart rate variability (FHRV), and movement (FM) assessed at 24, 30, and 36 weeks gestation and fetal genotype (from saliva samples after birth).
Results: Hierarchical linear modeling show a significant three-way interaction between time, maternal distress, and child genotype (p = .01) such that for fetuses with one risk allele (i.e., SL or SS), maternal distress was associated with a lack of the expected decrease in FHR across gestation. For FHRV there also was a similar significant three-way interaction (p = .03) such that for fetuses possessing one risk allele, SRI exposure was associated with a steeper increasing slope of FHRV, suggesting accelerated development.
Conclusions: These results indicate that for those with the risk allele maternal distress and psychotropic medication use exert subtle effects in opposite directions: distress was associated with a decrement of the developmental expectation while maternal medication use with an amplification.

Keywords: Perinatal Mental Health, SRI, Fetal Development, Serotonin Transporter Gene, Pregnancy
Supported by: P50 MH077928

41. Prenatal Anxiety and Child Immune Function

Thomas G. O'Connor

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Background: Prenatal maternal anxiety (or stress) has emerged as a leading paradigm for examining the developmental programming hypothesis for human health and development. Research findings from several labs show that anxiety or stress in pregnancy predicts neurocognitive and language difficulties, behavioral and emotional problems, and alterations in stress physiology. In the current study, we expand to outcome focus to immune function, an obvious clinical and public health concern as well as a plausible mechanism for the reported associations between prenatal anxiety and mental and somatic health.
Methods: A sample of 190 women, oversampled for prenatal anxiety, were assessed with clinical interview in the second and third trimesters; diurnal cortisol was also collected on these

occasions. Indicators of infant B-cell, T-cell and innate immunity were measured from blood samples obtained at 2-, 6-, and 16-months of age.
Results: No associations between prenatal maternal anxiety and infant immunity were detected at 2 months. However, reliable associations were found between prenatal maternal anxiety and infant immune markers from 6 months of age. For example, prenatal maternal anxiety predicted decreased IFN-gamma responder cell frequencies in response to hepatitis B surface antigen, a marker of T-cell or cell-mediated immunity, when the infants were 6 months ($r = -.29$, $p<.05$) and 16 months ($r = -.31$, $p<.05$) of age.
Conclusions: The findings suggest that there may be developmental programming effects on immune function and suggest an additional mechanism by which prenatal maternal anxiety may shape behavioral and somatic health in children.

Keywords: prenatal anxiety, immunology, child development, developmental programming, psychoneuroimmunology
Supported by: NIMH

42. The Lasting Influence of Early Intervention on the Methylome

Kieran J. O'Donnell[1], Chen Li[2], Katherine Beckmann[3], David Olds[4], Elena Grigorenko[5], James F. Leckman[5], Joanna D. Holbrook[2], Michael Kobor[6], Michael Meaney[1]

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Background: The persisting influence of childhood adversity on vulnerability for mental disorder is well established. Both animal models and clinical studies identify epigenetic regulation of genomic function as a plausible mediating mechanism. We have carried out the first epigenetic analysis of the effect of the Nurse Family Partnership (NFP), a perinatal parenting intervention with established treatment outcomes.
Method: We used the Humanmethylation450 Beadchip (Illumina) to measure genome-wide DNA methylation (methylome) in whole blood samples from participants (n=188, aged 27 years) born to women from treatment and control groups. Methylation data were corrected for cellular heterogeneity and batch effects. Principal component and regression analyses determined associations between DNA methylation, early intervention and child maltreatment.
Results: NFP treatment-associated with 1015 CpGs across 593 genes ($p<0.05$). Interestingly, treatment-associated CpGs showed significant enrichment for neurodevelopmental processes, including NOTCH-signaling (unadjusted $p= 3.84x10-5$; Bejamini-Hochberg adjusted $p=0.02$). We also observed a significant association between child maltreatment and variation in the methylome at 27 years of age independent of gender, ethnicity and the cellular heterogeneity of whole blood. History of maltreatment associated with 1552 variably methylated CpGs across 878 genes.
Conclusions: We provide some of the first evidence that early intervention associates with DNA methylation, while also demonstrating the persisting influence of child maltreatment on the methylome. These cross-sectional data emphasize a need to determine the developmental timing of these epigenetic changes and their role in mediating NFP program effects on child outcomes.

Keywords: Epigenetics, DNA methylation, Early intervention, child maltreatment, early life programming
Supported by: The Ludmer Centre for Neuroinformatics and Mental Health, CIFAR Child and Brain Development Program, Sackler Program for Epigenetics and Psychobiology

SYMPOSIUM
Neuroimaging Techniques in the Clinic

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Manitoba – Mezzanine
Chair: Quentin J.M. Huys*

***Supported by:** DFG RA1047/2-1

43. Structural and Functional MRI Predictors of Treatment Response in Depression

Cynthia H.Y. Fu[1,2]

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Background: Prognostic markers of clinical response from brain imaging have revealed multimodal effects within a frontostriatal-limbic network. In addition to the well replicated finding of increased anterior cingulate activity being predictive of clinical response, our meta-analysis revealed that activation in the insula and striatum as well as reduced hippocampal volume were predictive of a poorer clinical response.
Methods: Multimodal neuroimaging was acquired of emotional processing, resting state, and structural correlates of major depressive disorder (MDD) during an acute depressive episode and following 12 weeks of treatment with duloxetine. Subjects were MDD in an acute depressive episode (n=32; mean age 40.2 years) and healthy participants matched for age, gender, and IQ (n=25; mean age 38.8 years). Patients with MDD received treatment with duloxetine. All subjects underwent serial MRI scans at weeks 0, 1, 8, and 12.
Results: Reduced baseline resting state connectivity within the orbitofrontal component in the default mode network was associated with subsequent clinical response. A significant group by time interaction was identified in the anterior default mode network in which MDD patients showed increased connectivity with treatment while there were no significant changes in healthy participants. In the emotional Stroop task, increased posterior cingulate activation in MDD patients normalized following treatment. No significant group by time neural effects, including in amygdala responsiveness, were observed for happy or sad facial processing.
Conclusions: Resting state connectivity was predictive of clinical response, and multimodal functional and structural neuroimaging correlates demonstrated complementary effects of treatment.

Keywords: depression, fMRI, pharmacotherapy, prognosis, resting state
Supported by: HEFCE, Brain & Behaviour, Eli Lilly

44. EEG Biomarkers of Treatment Response in Major Depression

Dan V. Iosifescu

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Background: There is a clear need for objective biomarkers to assist and optimize the selection of efficacious antidepressant treatments in major depressive disorder (MDD), especially for subjects who failed previous treatments. We will review evidence suggesting that several quantitative electroencephalography (QEEG)-based technologies may be useful for predicting clinical response to antidepressants and for guiding treatment decisions.
Methods: We will review several clinical trials in MDD a 3 parameter QEEG index (the Antidepressant Treatment Response Index, ATR) was recorded prior to onset of antidepressant treatment and one week after onset as a predictor of antidepressant response. Also, an on-going randomized controlled study at Walter Reed Medical Center is testing the efficacy of PEER Interactive (a QEEG-based algorithm to guide antidepressant treatment selection) against treatment as usual (TAU).
Results: In several studies with more than 300 MDD subjects, ATR (measured at baseline and week 1) showed good ability (74% accuracy, AUROC=0.77) to predict clinical response to antidepressants such as escitalopram or buproprion after 8 weeks of treatment. In the first 109 MDD subjects randomized to PEER or TAU in the Walter Reed study, subjects following PEER-recommended treatment experienced significantly superior antidepressant effect (measured as change in QIDS-SR score from baseline and as reduction in suicidality scores on CHRT) over patients whose treatments did not follow the PEER report ($p<0.03$ for all analyses).
Conclusions: Several EEG technologies have the potential to offer reliable and relatively inexpensive predictors of treatment response in MDD. Additional studies are ongoing to validate the promise of these technologies.

Keywords: Major depression, QEEG, Predictor, Treatment Response
Supported by: CRADA WRNMMC 378604-12, CNS Response, Aspect Medical

45. Neurobehavioural Predictors of Relapse in Alcohol Use Disorders

Quentin JM Huys[1,2], Daniel Schad[3], Lorenz Deserno[4], Miriam Sebold[3], Maria Garbusow[3], Michael Smolka[5], Michael Rapp[3], Florian Schlagenhauf[4], Andreas Heinz[3], DFG "LEaD" Forschergruppe

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Background: Addictive drugs often prove too much of a temptation to resist, possibly because they undermine neural learning signals. Learning in Alcohol Dependence (LeAD) is a longitudinal study examining the contribution of model-based and model-free learning mechanisms in alcohol addiction and relapse, with the aim of generating valid predictors of relapse risk.
Methods: Longitudinal two-centre study of detoxified patients with alcohol use disorder. Participants and matched controls underwent fMRI with two tasks assessing the relative impact of model-based and model-free learning, and a Pavlovian-instrumental transfer (PIT) task. A separate set of controls also underwent F-DOPA PET. Patients were followed up for three months. For prediction, we used Leave-one-out-crossvalidation.
Results: Alcohol addiction was behaviourally accompanied by a shift towards away from model-based behaviour. There was a specific difficulty in re-establishing goal-directed control after losses. Measures of presynaptic dopamine synthesis capacity in the nucleus accumbens reduced model-free signals and promoted model-based learning. During PIT, patients showed an enhanced influence of Pavlovian stimuli on instrumental behaviour. In those patients who went on to relapse, this PIT behaviour was accompanied by the nucleus accumbens BOLD activity, whereas in others it was not. Critically, BOLD activity predicted relapse above chance (71% correct) and better than (a combination of) classical measures.
Conclusions: A broad shift towards model-free neural systems seen in several tasks and across methodologies indexes a prospective relapse risk for alcohol use disorders and is particularly accompanied by a preferential involvement of the nucleus accumbens. The results will be discussed with respect to clinical applicability.

Keywords: Alcohol use disorder, Decision-making, Model-based and model-free decisions, Pavlovian-Instrumental Transfer, Computational Psychiatry
Supported by: DFG FOR 1617

46. Imaging Predictors for the Development of Alcohol Use Disorders

Gunter Schumann

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Background: In the IMAGEN project we aim to identify the neurobiological basis of individual variability in reinforcement behaviour and determine their predictive value for the development of addictions and other psychiatric disorders.
Methods: Comprehensive behavioural and neuropsychological characterization, functional and structural neuroimaging and genome-wide association analyses of 2000 14-year-old adolescents at baseline are coupled with longitudinal follow-up at 16 and 19 years and combined with functional genetics in animal and human models.
Results: Here we present a machine learning approach, which we applied to generate models of current and future adolescent alcohol misuse that incorporate brain structure and function, individual personality and cognitive differences, environmental factors, life experiences, and candidate genes (Whelan et al.; 2014; Nature 512: 185-9). We will extend these results by evaluating the correlation of brain network activity with behavioural symptoms clusters within and across externalizing disorders, including alcohol use disorders using cognitive, emotional and environmental measures. To this end we will present data analyzing configurations of a

network of brain activity during reward anticipation, which we identified using weighted correlational network analysis, and which we correlated with behavioural symptoms.
Conclusions: We propose that this strategy promises to identify stratification markers based on specific neural mechanisms, thus targeting causal mechanisms, which underlie mental illness.

Keywords: Imaging genetics, externalizing disorders, alcohol use disorders prediction, stratification
Supported by: LSHM-CT-2007-037286, FP& IMAGEMEND and MATRICS, EAU-AIMS 115300-2, MRCPG 93558, FORMAS, eMED SysAlc, AERIAL, 1EVO711

ORAL SESSION
Developmental/Pediatric
Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Algonquin – Mezzanine
Chair: Eric M. Morrow

47. Childhood Abuse and Deprivation Have a Distinct Gender-Dependent Neural Morphology in a Healthy Sample

Daphne Everaerd[1,2], Floris Klumpers[2], Marcel Zwiers[3], Tulio Guadalupe[4], Barbara Franke[1,2,5], Iris van Oostrom[1,2], Aart Schene[1,2], Guillén Fernández[2], Indira Tendolkar[1,2,6]

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Background: Childhood adversity (CA) has been associated with an increased risk for psychiatric disorders and long-term structural differences in the brain. Recent evidence suggests that subtypes of CA, varying in the dimensions of threat and deprivation, may lead to distinct neural and behavioral outcomes. However, these specific associations have yet to be established without potential confounders such as psychopathology. Moreover, gender effects should be explored considering gender differences in neural development and psychopathology.
Methods: We used a whole brain optimized voxel-based morphometry approach to assess the gray matter (GM) differences associated with each specific subtype of abuse. We compared subjects (mean age 22 years) reporting exclusive childhood exposure to abuse (n=127, 46% males) or to deprivation (n=126, 41% males) and a group of matched controls (n=129, 44% males) without reported childhood events. Subjects were selected from a large (n>2800) sample of healthy adults.
Results: We found differences between CA-subtypes in the fusiform/ inferior temporal gyrus and middle occipital gyrus (P_{FWE}<0.05), where subjects with a history of deprivation had less GM than subjects with a history of abuse. Additionally, we found gender- CA-subtype interactions. Women showed less GM in the visual posterior precuneal region (P_{FWE}<0.01) after both subtypes of CA. Men had less GM in the postcentral gyrus (P_{SVC}<0.05) after childhood deprivation only.
Conclusions: Our results suggest that distinct CA subtypes are related to specific alterations in brain structure, which are modulated by gender. These findings may help guiding future research into the mechanistic underpinnings of psychopathology caused by childhood adversity.

Keywords: Childhood Adversity, Voxel Based Morphometry, Gender

48. Emotional Eating Mediates the Association Between Low Maternal Sensitivity and High BMI in Pre-School Girls but not Boys

Barbara E. Wendland[1], Leslie Atkinson[2], Patricia P. Silveira[3], Alison Fleming[4], Marla Sokolowski[5], Helene Gaudreau[3], Stephen Matthews[6], Meir Steiner[7], Michael Meaney[3], Robert Levitan[8]

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Background: Emotional Eating is a core feature of many eating and/or mood disorders, and causes significant medical and psychiatric morbidity over time. This study examined whether Emotional Eating mediates the recently demonstrated association between low maternal sensitivity experienced at age 6 months (based on the Maternal Behaviour Q-Sort or MBQS) and high BMIs in girls at age 4 years.
Methods: Current data are based on 223 children (boys: n=115; girls: n=108) participating in the Maternal Adversity Vulnerability and Neurodevelopment (MAVAN) project. Standard regression equations were used to test a mediation model.
Results: As previously reported, girls exhibited a significant negative correlation between MBQS scores at 6 months and BMIs at 48 months (r= -0.25, p=0.008). Consistent with our hypothesis, girls also exhibited a strong negative correlation between MBQS scores and Emotional Eating at 48 months (r= -0. 30, p=0.002). When both MBQS and Emotional Eating scores were entered into a single regression to predict 48-month BMI, the MBQS scores were no longer a significant predictor of BMI, supporting a mediation effect of Emotional Eating. These results were robust after controlling for maternal BMI and other covariates. No such effects were seen in boys.
Conclusions: In the MAVAN cohort, Emotional Eating mediates the relationship between low maternal sensitivity at 6 months of age and higher BMIs in girls at 48 months. These results may inform novel sensitivity-based preventative strategies for Emotional Eating, starting in the very first year of life.

Keywords: Emotional eating, Maternal sensitivity, Body mass index, Sex differences
Supported by: Faculty of Medicine McGill University; Norliein Foundation; WOCO Foundation

49. Overall Clinical Impairment Associated with Rare Copy Number Variants (CNVs) Associated with Neurodevelopmental Disorders

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Background: Overall clinical risk associated with rare neurodevelopmental disorder associated CNVs remains unknown and may be higher than realized due to as yet undiscovered pleiotropy. The primary goal of this study was to assess an overall burden of risk for very early-onset neuropsychiatric and possibly other pediatric disorders in general.
Methods: At the Children's Hospital of Pennsylvania (CHOP), over 100,0000 DNA samples are available from individuals aged 0-21 years, from the Philadelphia area for whom DNA is banked in their bio-repository from 16 pediatric clinics and the hospital. This population was assessed for five CNV regions: 2p16.3(NRXN1), 22q11, 15q13, 16p11, and 2p25.3 (PDNX/MYT1L) using Taqman PCR assay. These are of particular interest to us, as they were over-represented in the COS studies compared to adult schizophrenia patients. Each individual with an identified CNV was compared to five controls without CNVs in the examined regions. Each group is matched for age, sex, ethnicity, mother's education, and locality, with local individuals defined as living within 50 miles of CHOP.
Results: For the initial 40,000 pediatric subjects screened, 16p11 del carriers had more Endocrine/nutritional metabolic/immunity disorders than did controls (P=0.0018). Also 16p11 del/dup carriers and 22q11 dup carriers had more surgery than did controls (P<0.0028). Notably, 22q11 dup increases digestive problems such as Gastro esophageal reflux disease (**GERD**) (P=0.00048). Finally, the prevalence of mental problems was higher than control for 16p11 del carriers and 22q11 dup carriers (P<0.0005).
Conclusions: The overall clinical risk for carrying a CNV appears to be quite broad, and these findings would provide a better estimate for genetic counseling.

Keywords: copy number variants, neurodevelopmental disorders

50. High Rates of Prodromal Negative Symptoms in 22q11.2 Deletion Syndrome Compared to Williams Syndrome and to Typically Developing Controls

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Background: 22q11.2 deletion syndrome (22q11DS), also known as velo-cardio-facial syndrome (VCFS) or DiGeorge syndrome is the most common genetic syndrome associated with schizophrenia. About one-third of individuals with 22q11DS develop schizophrenia by early adulthood. Therefore it is important to identify early signs of psychosis in this population, a task which is complicated by the intellectual disabilities that are common in 22q11DS. The purpose of our study was to identify the prodromal symptoms that are characteristic of 22q11DS in comparison to Williams Syndrome (WS) and to typically developing (TD) controls.
Methods: Age and gender matched adolescents and young adults with 22q11DS (n=51), WS (n=20) and TD controls (n=23) underwent extensive psychiatric and cognitive evaluations and the Structured Interview for Prodromal Symptoms (SIPS).
Results: Both 22q11DS and WS had significantly higher rates of prodromal syndromes compared to TD. The 22q11DS and WS groups had similar rates of prodromal syndrome based on the positive symptoms. When including the negative and disorganized symptoms, the 22q11DS had significantly higher rates of prodromal syndrome compared to WS (42.5% vs. 15.0%, p=0.044). Reports of probands and caregivers were higher in 22q11DS compared to WS on several negative scales including avolition, decreased expression of emotion, decreased experience of emotion and self, and deterioration in role functioning.
Conclusions: Our results suggest that in terms of prodromal symptoms, negative symptoms, and not positive symptoms, distinguish individuals with 22q11DS from individuals with another developmental disability. Those negative symptoms in 22q11.2DS youngsters potentially predict the evolution of psychotic disorders.

Keywords: 22q11DS, schizophrenia, clinical trial, SIPS, prodrome
Supported by: The Binational Science Foundation (grant number 2011378) and the National Institute of Mental (5U01MH101722-02)

51. Disruption of Thalamocortical Connectivity in Neonates with Prenatal Cocaine Exposure and its Interaction with SSRIs

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Background: Prenatal cocaine exposure (PCE) has significant cognitive, behavioral, and physiological impacts during early development. Mechanistically, cocaine readily crosses the placenta to interfere with fetal dopamine (DA) systems. The thalamus, being DA-receptor-rich, is vulnerable to cocaine insults but the establishment of normal thalamocortocal connectivity is key in early development. In this study we explored the effects of cocaine and other drugs on thalamocortical connectivity by investigating neonates exposed to cocaine and other drugs (PCE), only non-cocaine drugs (NCOC), and drug free controls (CTR).
Methods: 152 neonates (~ 3weeks of age, PCE = 45, NCOC = 43, CTR = 64) were imaged using fMRI. Thalamocortical connectivity from the anterior and posterior thalamus seeds was compared across groups controlling for birth age, birth weight, scan age, gender, and scanner to detect drug-exposure related differences. Further drug specificity/interaction analyses were also conducted.
Results: Three salience-network related prefrontal clusters demonstrated hyper-connectivity in the PCE group (Figure 1). PCE and NCOC showed common disruptions in a motor-related cluster. In addition, cocaine effects were significantly enhanced by selective serotonin reuptake inhibitors (SSRIs), producing a significant interaction effect after controlling for maternal depression.
Conclusions: Findings from this study revealed abnormal thalamocortical functional connectivity associated with PCE and provided

the first human-based evidence of cocaine*SSRI interactions, calling for more cautions in the prescription of SSRIs to pregnant women with cocaine dependencies.

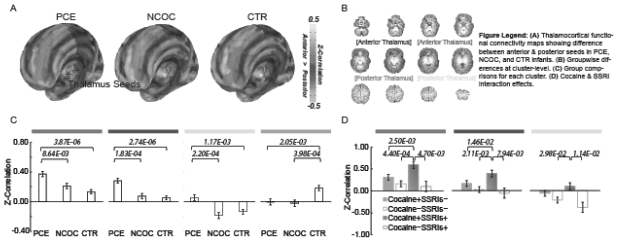

Figure Legend: (A) Thalamocortical functional connectivity maps showing difference between anterior & posterior seeds in PCE, NCOC, and CTR infants. (B) Groupwise differences at cluster-level. (C) Group comparisons for each cluster. (D) Cocaine & SSRI interaction effects.

Keywords: Prenatal Cocaine Exposure (PCE), Thalamocortical Connectivity, fMRI, Infants, SSRIs
Supported by: R03 DA036645-01A1; P01DA022446

52. Maternal Self-Reported Antenatal Depressive Symptoms Predict Infant NR3C1 1F And BDNF IV Methylation

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Background: Prenatal psychological distress increases risk for adverse infant outcomes. However, the biological mechanisms underlying this associationremain unclear. Prenatal stress can impact fetal epigenetic mechanisms thatcould underlie changes in infant stress responses. This may be, in part,mediated by maternal glucocorticoids. To address this, we examined the impactof maternal cortisol and depressive symptoms during pregnancy on infant *NR3C1* DNA methylation, and explored the novel hypothesis that infant *BDNF* DNAmethylation may be impacted by maternal antenatal depression.
Methods: 57 pregnant women were recruited during the second or third trimester. Participants self-reported depressive symptoms and salivary cortisolsamples were collected diurnally, at awakening, and in response to a stressor. Buccalswabs for DNA extraction and DNA methylation analysis were collected from each infant at two months of age, and mothers reported postnatal depressive symptoms.
Results: In male infants, antenatal depressive symptoms significantly predicted increased *NR3C1* 1F DNA methylation (β=2.147,p<0.05). Antenatal depressive symptoms also significantly predicted decreased *BDNF* IV DNA methylation in both male and female infants (β=-3.244,p<0.01). No measure of maternal cortisol during pregnancy predicted infant *NR3C1* 1F or *BDNF* IV DNA methylation.
Conclusions: Our findings highlight the susceptibility of males to changes in *NR3C1* DNA methylation following exposure to antenatal depression, and provide evidence that antenatal depression results in decreased infant *BDNF* IV DNA methylation. The lack of association between maternal cortisol and infant DNA methylation suggests that effects of maternal depression may not be mediated directly by glucocorticoids. Future studies should consider other potential mediating mechanisms in the link between maternal mood and infant outcomes.

Keywords: Antenatal depression, Epigenetics, NR3C1, BDNF
Supported by: Medical Research Council

53. Impaired Fear Extinction Retention in Adolescence: Age at Fear Learning or Age at Extinction?

Kathryn D. Baker, Rick Richardson

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Background: Fear inhibition is markedly impaired in adolescent rodents and humans. The present experiments investigated whether this impairment is critically determined by the animal's age at the time of fear learning or their age at fear extinction.
Methods: Male rats (n = 163) were tested for extinction retention after conditioning and extinction at different ages. We examined neural correlates of impaired extinction retention by detection of phosphorylated mitogen activated protein kinase immunoreactivity (pMAPK-IR) in several brain regions.
Results: Unexpectedly, adolescent rats exhibited good extinction retention if fear was acquired before adolescence. Further, fear acquired in adolescence could be successfully extinguished in adulthood but not within adolescence. Adolescent rats did not show extinction-induced increases in pMAPK-IR in the medial prefrontal cortex or the basolateral amygdala, or reduced caudal central amygdala activity, as was observed in juveniles. This dampened prefrontal and basolateral amygdala activity following extinction in adolescence occurred even when there was no impairment in extinction retention. In contrast, only the adolescent animals that exhibited impaired extinction retention showed elevated pMAPK-IR in the posterior paraventricular thalamus.
Conclusions: Neither the animal's age at the time of fear acquisition or extinction determines whether impaired extinction retention is exhibited. Rather, it appears that forming competing fear conditioning and extinction memories in adolescence renders this a vulnerable developmental period in which fear is difficult to inhibit. Furthermore, even under conditions which promote good extinction, the neural correlates of extinction in adolescence differed to those recruited in animals of other ages.

Keywords: Extinction, Fear, Adolescence, Medial Prefrontal Cortex, Amygdala
Supported by: ARC DP120104925; NHMRC project grant APP1031688; UNSW Science FRG; NHMRC Early Career Fellowship APP1054642

54. Neural and Behavioral Vigilance Patterns in the Laboratory Predict Real-World Avoidance Among Anxious Youth

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Background: Vigilance and avoidance of threat are (a) observed in anxious individuals during laboratory tasks and (b) posited to have real-world clinical relevance. Vigilance is hypothesized to foster

anxiety, prompting the use of avoidance as a maladaptive coping strategy, but previous studies have not assessed whether laboratory-assessed vigilance predicts real-world avoidant behavior. Impaired functional connectivity between the amygdala and prefrontal cortex (PFC) is a posited neural substrate of laboratory-assessed vigilance that may also promote maladaptive avoidance behavior in ecological settings.
Methods: 78 clinically anxious youth completed a dot-probe task to assess vigilance to threat (fearful faces) while undergoing functional MRI. Real-world avoidance patterns were assessed over 4 subsequent days using Ecological Momentary Assessment (EMA) of self-reported avoidance and distraction.
Results: Greater behavioral vigilance towards threat was associated with greater EMA avoidance (r=.27, p=.01) and distraction (r=.23, p=.04). In a whole-brain search, functional connectivity between a right amygdala seed region and dorsomedial PFC during the dot-probe was inversely related to EMA distraction (r=-.49, p<.001), and statistically mediated the relationship between vigilance and real-world distraction use.
Conclusions: Anxious youth showing vigilance towards threat in the laboratory are more likely to rely on avoidance and distraction in ecological settings. Decreased PFC control over limbic reactivity is a possible neural substrate of this vigilant-avoidant pattern. Given growing interest in mechanistic treatments targeting attentional patterns, these findings lend real-world validity to laboratory vigilance assessments in youth and suggest top-down limbic regulation is a neural mechanism relevant in both laboratory and ecological contexts.

Keywords: vigilance, avoidance, functional MRI, anxiety, attentional bias
Supported by: K23MH100259; MH080215

ORAL SESSION
Neuromodulation

Thursday, May 14, 2015, 12:30 PM – 2:30 PM
Tudor 8 – Main Mezzanine
Chair: Seong S. Shim

55. Deep Transcranial Magnetic Stimulation in Obsessive Compulsive Disorder (OCD) patients

Lior Carmi[1], Joseph Zohar[2], Reuven Dar[1], Uri Al Yagon[3], Abraham Zangen[3]

[1]Psychology, Tel Aviv University, Tel Aviv, Israel, [2]Sackler faculty of medicine, Tel Aviv University, Tel Aviv, Israel, [3]Life Sciences, Ben Gurion university, Beer-Sheva, Israel

Background: Characterized by compulsive rituals and Obsessive thoughts, OCD is a chronic and disabling disorder. Despite converging evidence pointing towards the involvement of dysfunctional cortico-striato-thalamo-cortical (CSTC) circuit in OCD, the neurophysiological pathology of OCD is still not well characterized. Indeed, 40%-60% of patients do not respond adequately to standard treatments. Transcranial magnetic stimulation (TMS) is a noninvasive therapeutic technique, recently applied to treat and investigate OCD. However, lacking the ability to target the CSTC circuit directly, standard TMS treatment protocols for OCD showed diversified results. The use of special deep TMS (dTMS) coils allows direct stimulation of deeper neuronal pathways relative to those affected by standard TMS coils. Here we evaluated whether dTMS targeting the medial prefrontal and the anterior cingulate cortices may influence symptom severity.
Methods: 40 OCD patients were treated with either dTMS or a sham coil for five weeks in a double-blind controlled study. The patients were divided into groups receiving either high (20Hz) or low (1Hz) stimulation frequencies, and were simultaneously administrated with symptom provocation. EEG measurements were taken at baseline and at the end of treatment.
Results: The active 20Hz dTMS group improved significantly in YBOCS score compared to the 1Hz and placebo groups (28% vs. 6% reduction), {t (93) = -2.29 (p=0.0243)}. Moreover, follow-up assessments revealed 3 months stability in improvements as measured by the YBOCS scores. EEG evoked responses measured over the anterior cingulate cortex correlated with clinical response.
Conclusions: High frequency dTMS treatment, targeting the medial prefrontal and the anterior cingulate cortices is a promising therapeutic intervention in OCD.

Keywords: OCD, Deep TMS, ACC
Supported by: Brainsway

56. Transcranial Magnetic Stimulation of Left Dorsolateral Prefrontal Cortex for a Major Depressive Episode Increases Brain Volume in Specific Cortical Regions

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Background: Repetitive transcranial magnetic stimulation (rTMS) is an approved antidepressant treatment but little is known of its mechanism of action. Specifically, downstream effects of rTMS remain to be elucidated. To our knowledge, this is the first study of structural changes during rTMS treatment of depression.
Methods: 27 patients in a DSM-IV current major depressive episode and on a stable medication regimen, had a 3T magnetic resonance T1 structural scan before and after five weeks of standard TMS treatment to the left dorsolateral prefrontal cortex. Voxel-based morphometry was performed using high dimensional non-linear diffusomorphic anatomical registration (DARTEL) to identify changes with treatment.
Results: Anterior cingulate, cingulate body, precuneus, insula (right only) and medial frontal gyrus gray matter volumes increased with treatment (range: 5.3% to15.7%). No region decreased in volume. >92% of subjects had increases in gray matter volumes in all of these brain regions. The changes did not correlate with clinical antidepressant response.
Conclusions: rTMS appears to have a neuroplastic effect in brain areas involved in cognitive appraisal, subjective experience of emotion and self-referential processing, all of potential relevance to its antidepressant effect.

Keywords: Transcranial Magnetic Stimulation, Major Depressive Disorder, Magnetic Resonance Imaging, Voxel Based Morphometry, Emotion appraisal
Supported by: BBRF Young Investigator Award; K23MH104688; K99MH097822

57. Transcranial Direct Current Stimulation for Major Depression: A Meta-analysis of Individual Patient Data

Andre Brunoni[1], Adriano Moffa[1], Felipe Fregni[2], Ulrich Palm[3], Frank Padberg[3], Daniel M. Blumberger[4], Zafiris J. Daskalakis[4], Djamila Bennabi[5], Emmanuel Haffen[5], Angelo Alonzo[6], Colleen K. Loo[6]

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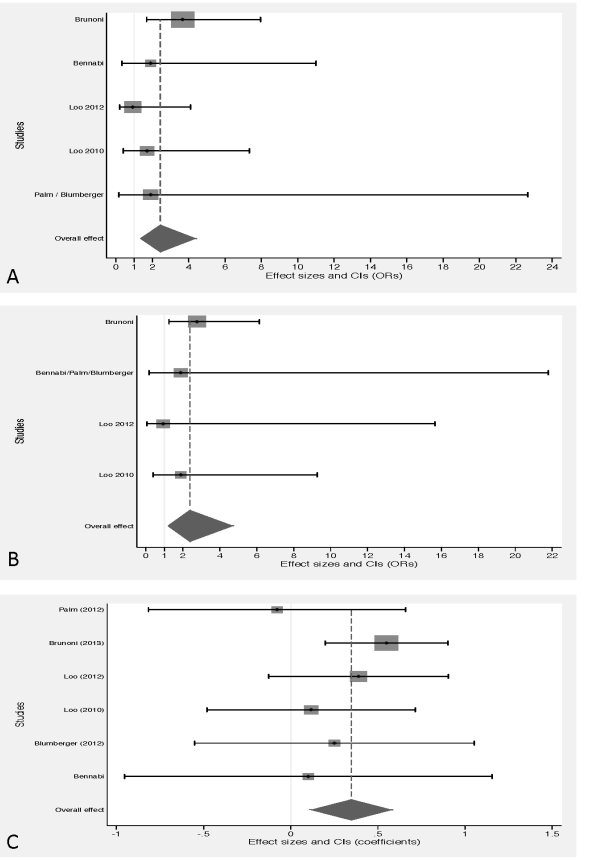
Background: Transcranial direct current stimulation (tDCS) is a putative non-pharmacological therapy for depression, although results are mixed, possibly due to the heterogeneity of the study samples.

Methods: We used a meta-analytic approach of individual patient data from six recent randomized sham-controlled trials, enrolling 289 patients. Using this approach, we could provide parameters of efficacy and explore further the predictors of tDCS response by assessing individual clinical, demographic and treatment characteristics.

Results: Active tDCS was superior to sham for response (34% vs. 19%, respectively; OR=2.44, 95%CI 1.38-4.32, p<0.01), remission (23.1% vs. 12.7%, respectively, OR=2.38, 95%CI 1.22-4.64, p<0.01) and depression improvement (linear B coefficient (z-scores)=0.35, 95%CI= 0.12-0.57, p<0.01). Mixed-effects models showed that, after adjustment for other significant predictors and confounders, including methodological differences from the six studies, treatment-resistant depression and higher tDCS "doses" (calculated based on current density, session duration and number of sessions) were respectively negatively and positively associated with tDCS efficacy.

Conclusions: The findings from our individual patient data meta-analysis confirm the efficacy of tDCS: its treatment is associated with a NNT of 6.67 for response, similarly, for instance, to antidepressant drug treatment in primary care and repetitive transcranial magnetic stimulation treatment. Furthermore, the two most important parameters that need to be controlled, assessed and/or adjusted in future larger trials are treatment resistance and tDCS dose



Keywords: transcranial direct current stimulation, major depressive disorder, meta-analysis, individual patient data, non-invasive brain stimulation

58. Functional and Structural Neuroplasticity Possibly Induced by a Series of Prefrontal rTMS for Major Depression

Motoaki Nakamura[1,2,3,4], Yoshihiro Noda[5], Takashi Saeki[2], Shunsuke Hayasaka[2,4], Takuji Izuno[3], Takuya Yoshiike[1], Shuichi Morinaga[1], Yoshio Hirayasu[2]

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Background: Neuroplasticity possibly induced by repetitive transcranial magnetic stimulation (rTMS) on dorsolateral prefrontal cortex (DLPFC) were longitudinally investigated in major depression, using MRI, diffusion tensor imaging (DTI), and quantitative EEG (qEEG).

Methods: Patients with major depression underwent 10 daily 20-Hz rTMS sessions over left DLPFC during two weeks. Efficacy was evaluated with the Hamilton Depression Rating Scale 17-item (Ham-D17).
Results: Voxel-based morphometry (VBM) (n=38) revealed that rTMS on left DLPFC could increase gray matter volume in left DLPFC (t=5.53, P_{FWE}=0.034). Responders (n=27) showed gray matter volume increase in left DLPFC (t=6.73, P_{FWE}=0.002) and left anterior cingulate cortex (t=4.52, P_{FWE}=0.021), left subgenual cingulate cortex (t=3.61, P_{FWE}=0.05) compared to non-responders (n=11), who showed less than 25% improvement from baseline score of Ham-D17. Voxel-based analyses of DTI (n=21) revealed that rTMS could decrease "gray matter" mean diffusivity in bilateral DLPFC (left: t=8.21, P_{FWE}=0.002, right: t=7.37, P_{FWE}=0.009). Resting-state qEEG (n=31) showed longitudinal enhancement of spectral power of gamma band oscillations at left frontal region (t=3.09, P=0.004) and the modulation index which reflects theta-gamma coupling (t=2.48, P=0.019) over 10 rTMS sessions.
Conclusions: Following 10 rTMS sessions over two weeks, gray matter showed increased volume with decreased mean diffusivity longitudinally around the stimulation site. The present findings suggest that rTMS may increase neuropil contents in the stimulation site as well as associated para-limbic region, possibly relating to its antidepressant effect and structural neuroplasticity. Increase of gamma power and theta-gamma coupling at resting-state could suggest rTMS-induced enhancement of functional neuroplasticity.

Keywords: repetitive transcranial magnetic stimulation, neuroplasticity, prefrontal, theta gamma coupling, MRI
Supported by: the Ministry of Education, Culture, Sports, Science and Technology (MEXT)

59. Re-evaluating the Electroconvulsive Therapy Stimulus: Frequency and Directionality

Angel V. Peterchev, Christopher Sikes-Keilp, Moacyr A. Rosa, Sarah H. Lisanby

Psychiatry and Behavioral Sciences, Duke University, Durham, NC

Background: The electrical stimulus characteristics in electroconvulsive therapy (ECT) can affect its therapeutic efficacy and side effects. The conventional ECT stimulus is bidirectional, consisting of pulses of alternating positive and negative polarity. The pulse train frequency, together with its duration, is typically used to adjust the ECT dose. We investigated (1) what the optimal frequency for seizure induction is and (2) whether unidirectional stimuli have lower seizure threshold (ST) than bidirectional stimuli.
Methods: Subjects were four male *Macaca mulatta*. Study 1: ST was titrated at fixed frequencies of 5, 10, 16, 25, 50, 100, and 240 pulses per second (pps) with right unilateral (RUL) electrode placement. Study 2: ST was titrated with bidirectional, unidirectional-anodal, and unidirectional-cathodal pulse trains for RUL, bifrontotemporal, bifrontal, and frontomedial electrode placements. Each condition was repeated 3 times per subject.
Results: Study 1: ST had a significant, U-shaped dependence on the stimulus frequency ($F(6,72.08) = 50.04$, $p < .0001$). ST was lowest at 16 pps, with no significant difference among frequencies of 10-25 pps. The stimulus train duration at ST decreased monotonically with frequency. Study 2: There was no significant difference in ST between bidirectional stimuli and unidirectional stimuli of either polarity.
Conclusions: The optimal frequency for seizure induction, 16 pps (8 Hz), is below the minimum available in standard ECT devices (10-20 Hz). Unidirectional trains are not an effective strategy to reduce ST for the stimulation parameters considered. The relation between stimulus characteristics optimal for seizure induction and clinical outcome requires further study.

Keywords: ECT, frequency, directionality, stimulus, seizure threshold
Supported by: R01MH091083; R01MH060884

60. Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression: A Report on Long-term Safety and Efficacy

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Background: Deep brain stimulation of the subcallosal cingulate white matter (SCC DBS) is an experimental intervention for treatment-resistant depression. We report long-term, longitudinal follow-up in patients implanted at Emory University under a single site protocol (CT.Gov # NCT00367003).
Methods: Twenty-eight subjects with chronic treatment-resistant depression were enrolled from 2007 to 2013. Following a 1-month post-surgical recovery period, patients received continuous DBS using standard parameters (130 Hz, 90us, 6-8mA) with adjustments made based on failure to meet response criteria (50% reduction in HDRS17).
Results: All 28 subjects (mean age = 44.64; 19 females) received a minimum of one year of continuous DBS. Long-term follow-up data were available for a subset of subjects up to 6 years post-implantation. DBS responders showed maintenance of response over time, with only transient, reversible symptoms with discontinuation of stimulation. Current (mA) requirements did not vary or habituate with long-term delivery, and there were no stimulation-related adverse events. Device-related SAEs were infrequent and generally due to surgical or hardware problems, without permanent sequelae. There were no completed suicides. Three patients requested to be explanted.
Conclusions: This open label, single site study demonstrates sustained antidepressant effects of chronic SCC DBS out to 6 years. The treatment is well tolerated, without late developing adverse effects. These data provide support of the clinical potential of this technology for otherwise treatment-resistant depressed patients.

Long term follow-up in SCC DBS for TRD

	1 year	2 years	3 years	4 years	5 years	6 years
Number of Subjects	28	23	20	15	14	10
Number of Responders (%)	16 (57.1)	17 (73.9)	15 (75)	10 (66.7)	11 (78.6)	8 (80)
Number of Remitters (%)	10 (35.7)	8 (34.8)	8 (40)	7 (46.7)	6 (42.8)	4 (40)
Decrease in HDRS17 from baseline, in %	51	56.9	57.2	57.4	61.4	59.5

Keywords: Deep Brain Stimulation, Subcallosal Cingulate, Treatment-resistant Depression

61. Right Prefrontal Deep TMS Effects on Attention Symptoms: Behavioral Outcomes and Electrophysiological Correlates

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Background: Despite its high prevalence, the validated treatment for ADHD is chronic administration of psychostimulants, which is associated with side effects and occasionally not tolerated. Deep TMS using special coil designs for targeting neural networks linked with neuropsychiatric disorders, may become a viable alternative.
Methods: In the current randomized, sham-controlled study, adult ADHD patients received 15 daily sessions of high-frequency repetitive TMS directed to the right prefrontal cortex (rPFC), using either deep, figure-8, or a sham coil. ADHD symptoms and cognitive alterations were assessed using the CAARS-INV, self- report questionnaires and performance tests. Additionally, the stop signal task (SST) combined with EEG measures was used to asses behavioural inhibition and ERPs. EEG responses to an inhibitory protocol of paired TMS pulses over the rPFC were measured before and after treatments. A comparison group of healthy subjects was evaluated without receiving TMS treatment.
Results: Improvements in several measures of attention were observed in patients that received dTMS but not standard figure-8 or sham treatment (p=0.007, CAARS; p=0.014, SST). Differences between ADHD patients and healthy controls were demonstrated in ERPs during the SST, and in response to single and paired TMS pulses. The lower amplitudes of ERPs in patients correlated with ADHD symptoms and behavioural inhibition measures.
Conclusions: These findings suggest that repeated stimulation of deep areas in the rPFC has therapeutic potential, where rPFC excitability is impaired in ADHD patients. Ongoing analysis is attempting to make use of the mentioned neurophysiological measures as predictors and biomarkers for effectiveness of dTMS treatment.

Keywords: ADHD, Deep TMS, EEG

62. tDCS Elevates Human Prefrontal NAA: An Online tDCS/MRS Study”

Antoine Hone-Blanchet[1], Shirley Fecteau[1], Richard A. E. Edden[2]

[1]Medicine, Université Laval, Quebec City, QC, Canada, [2]Radiology and radiological science, Johns Hopkins School of Medicine, Baltimore, MD

Background: Transcranial direct current stimulation (tDCS) applied to the dorsolateral prefrontal cortex (DLPFC) can modulate behaviors, however the neural effects of such modulation during stimulation remain unknown. The objective of our study was to measure the neurobiological effect of a single, mild tDCS dose in real-time using magnetic resonance spectroscopy (MRS).
Methods: We conducted a crossover, double blind, sahm-controlled online protocol combining tDCS and MRS in 15 healthy subjects. We measured concentration levels of N-acetylaspartate (NAA), a marker of neuronal integrity and cell functioning, within the left DLPFC and striatum, during and immediately after tDCS delivery, with the anode and cathode electrodes over the left and right DLPFC, respectively.
Results: Our results show that active as compared to sham tDCS applied to the DLPFC elevates NAA (Wilcoxon Signed Ranks Test; p= 0.041) during tDCS. This effect was no longer significant immediately after tDCS (p= 0.795). Active tDCS had no effect on NAA levels in the left striatum during or after tDCS.
Conclusions: These observations indicate that tDCS over the DLPFC has fast excitatory effects on neuronal metabolism. This may partly explain its reported actions on neurotransmission, and such effects may contribute to its behavioral and clinical effects. The low dosage of delivered tDCS may explain the lack of effect over distal striatal neurons down the corticostriatal pathway.

Keywords: transcranial direct current stimulation, magnetic resonance spectroscopy, dorsolateral prefrontal cortex, n-acetylaspartate

SYMPOSIUM
NIMH Brains-Supported Research on Early Life Stress and Neurodevelopmental Mechanisms of Mental Illness Risk

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
British Columbia – Mezzanine
Chair: Christopher Sarampote
Co-Chair: Kathleen C. Anderson

63. Impact of Early Life Stress on Myelination and the Developing Brain

Daniela Kaufer

Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA

Background: Studies of myelin biology are increasingly seen as relevant to circuit models of major psychiatric disorders given the critical importance of structural connectivity across multiple brain structures. The process of myelination in the brain begins early in embryonic development and continues throughout development through late adolescence and adulthood. 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 adults rodents exposed to stress, and neurogenesis, oligodendrogenesis and myelination rates quantified in multiple brain areas. Transcriptional programming of the neural stem cells studied in adult hippocampal stem cell cultures.
Results: Exposure to stress in an adult rat redirected the developmental fate of adult neural progenitor/stem cells (NSC) in the dentate gyrus, a gray matter structure, yielding a decrease in neurogenesis and an increase in oligodendrogenesis (Chetty et al, Mol Psych, 2014). In vitro, treatment of NSCs with the stress hormone glucocorticoid induced a pro-oligodendrogenic transcriptional program and resulted in a shift in differentiation from a neuronal to oligodendrocytic fate. Furthermore, exposure to adverse early life stress increases oligodendrogenesis and myelin in the dentate gyrus.

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

Keywords: Stress, Adult neural stem cells, myelin, white matter, early life stress
Supported by: NIMH BRAINS (MH087495) award to DK

64. Hierarchical Development of the Human Neurobiology involved in Aversion-Learning

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Background: Learning about danger begins early in life, despite the slow neurobiological development that supports mature forms of learning. The current functional magnetic resonance imaging (fMRI) study used a basic aversive learning paradigm to examine neuro-hierarchical changes during aversion conditioning.
Methods: An aversive conditioning discrimination paradigm was administered to 91 healthy participants (4-23 years-old) during fMRI scanning. The paradigm presented one of two visual cues that either co-terminated (conditioned stimulus; CS+) with an aversive stimulus, or did not (CS-). Learning was assessed by both discrimination in galvanic skin response (GSR) to the CS+ and by changes in an operant-learned reaction time (RT) (i.e., slope-analysis).
Results: Discrimination learning was evident beginning in early childhood as measured by GSR and negatively sloped RT to the CS+ (with a temporary attenuation during adolescence). There were age-related changes in the neurobiology associated with aversive learning. Learning in adulthood recruited the amygdala and ventromedial prefrontal cortex (vmPFC) and strong amygdala-hippocampal functional connectivity. Learning in early childhood was characterized by robust amygdala recruitment, but neither hippocampal nor vmPFC engagement. Functional connections between the amygdala and the vmPFC and hippocampus began to emerge in the adolescent group.
Conclusions: Staggered development of the amygdala relative to the vmPFC and hippocampus was observed despite evidence for early discrimination learning, suggesting that aversive learning is supported by different neural mechanisms during development. These findings inform how fear-related processes operate uniquely at different ages across development and constraint interpretations about trajectories following highly-fearful early environments.

Keywords: Amygdala, Human, prefrontal cortex, hippocampus, child
Supported by: NIMH (R01MH091864, BRAINS Award); The Dana Foundation; Frontiers of Innovation – Harvard Center for the Developing Child

65. Telomere Length as an Epigenetic Indicator of the Transgenerational Impact of Early Life Adversity

Stacy Drury[1], Kyle Esteves[2], Katherine Theall[3]

[1]Tulane University, [2]Psychiatry, Tulane University, New Orleans, LA, [3]Public Heath, Tulane University, New Orleans, LA

Background: Telomere length (TL) is increasingly recognized as a biological indicator of stress associated with a range of negative health outcomes. As epigenetic factors are one hypothesized mechanism by which early adversity is biologically embedded and transmitted across generations this study tested the association between maternal adverse childhood events before the age of 18 and TL in her newborn child.
Methods: Pregnant mothers were interviewed about their own exposure to adverse childhood events. TL was determined using MMQ-PCR on DNA extracted from newborn screen blood spots (n=72). Other covariates were obtained via maternal report and medical records.
Results: Controlling for infant birth weight TL was significantly shorter in infants whose mothers reported living with a mentally ill family member before the age of 18 ($p=.05$, mean 1.68 compared to 1.82). Even after co-varying for maternal age, race, infant sex and birth weight the model remained significant ($p=.04$, $r^2=0.19$).
Conclusions: TL dynamics are increasingly being associated with a range of psychosocial and environmental stressors, potentially linked to persistent negative health consequences and health disparities. Importantly newer data suggests that telomeres function as global epigenetic regulators across the genome and their role in cellular function may go beyond current models of senescence and apoptosis to include cellular differentiation and more global markers of cellular function and stress responsiveness. Our findings linking maternal early adversity with newborn telomere length suggest that enhanced understanding of telomere dynamics may provide novel insights into the biological pathways impacted by early adversity.

Keywords: Telomere, early adversity, transgenerational, racial differences, infancy
Supported by: R01MH101533, BRAINS Award

66. The Developmental Origins of the Social Origins of Depression

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[1]Department of Social and Behavioral Sciences and Department of Epidemiology, Harvard School of Public Health, Boston, MA, [2]Center for Infection and Immunity, Columbia University, New York, NY, [3]Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Boston, MA

Background: Depression disproportionately burdens economically disadvantaged individuals. We investigated the early life origins of social inequalities in depression and explored neurodevelopmental explanations for these inequalities in the New England Family Study (n=1,258).
Methods: First, the impact of socioeconomic disadvantage on maternal immune functioning during pregnancy, a known contributor to deficits in brain development, was studied by analyzing concentrations of 5 cytokines in mid-gestation maternal serum

(interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α). Second, we investigated the impact of socioeconomic disadvantage and prenatal immune functioning on offspring neural development during childhood, based on clinical examinations conducted in childhood. Third, we studied the long-term associations of parental socioeconomic conditions and prenatal immune activity with major depression in offspring during adulthood.
Results: Maternal immune functioning during pregnancy was significantly associated with the level of maternal socioeconomic disadvantage. The most economically disadvantaged pregnancies had suppressed levels of the cytokine, IL-8 (-1.53 pg/mL on the logarithmic scale; CI=-1.81, -1.25). Socioeconomic disadvantage also increased the risk of clinically detectable neurologic abnormalities at 4 months (odds ratio (OR)=4.61; CI=2.84, 7.48) and 1 year of age (OR=2.05; CI=1.08, 3.90), partly due to variations in maternal prenatal IL-8. Finally, mid-gestational maternal immune status was significantly associated with offspring depression (OR for low TNF-α in maternal serum=1.46; CI=1.02, 2.10).
Conclusions: These findings support a prenatal stress-immune interaction model of depression pathogenesis, and suggest that the neurodevelopmental consequences of the intrauterine and early childhood early environment are clinically recognizable in early childhood.

Keywords: Depression, Prenatal, Cytokine, Epidemiology, Fetal Origins
Supported by: NIH grants MH087544 ("BRAINS" award to SEG), MH082679 (JMG), and MH07467 (JMG)

SYMPOSIUM
Orchestrating Synaptic and Extrasynaptic Glutamate Signaling: Implications for Schizophrenia and Addictive Behaviors

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Confederation 5/6 – Mezzanine
Chair: Doo-Sup Choi*
Co-Chair: Robert McCullumsmith

***Supported by:** R01AA18779

67. Abnormalities of Intracellular Signaling in Schizophrenia

Robert McCullumsmith

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Background: It is an understatement to say that the treatment of schizo-spectrum disorders has not progressed in the past 20 years, since the development of atypical antipsychotics. However, there is broad consensus that these newer medications do not extend the efficacy of pharmacological treatments to cognitive and negative/deficit symptoms, which lead to profound disability in a large number of persons afflicted with schizophrenia. To address this problem, we have adapted a novel "omics" approach to identify possible substrates for the development of new therapies. We hypothesize that abnormalities of intraceluular signaling underlie many of the cognitive deficits observed in theschizophrenia.
Methods: We used kinome array profiling and biochemical assays to investigate changes of signaling networks in the prefrontal cortex.
Results: We found changes in 19 reporter peptides from the kinome array, yielding several upstream kinases that survived permutation analyses for false positives. We used these hits to generate network models for changes in schizophrenia. We confirmed changes in activity of two implicated kinases, AKT and JNK, using specific kinases assays. Inhibitor studies suggest profound changes in signaling networks containing these kinases in schizophrenia. We also identified a SNP in the 5'UTR of the AKT1 gene that is associated with alterations of AKT activity in schizophrenia.
Conclusions: These innovative studies have identified signaling pathways disrupted in schizophrenia and provide new substrates for diagnosis and treatment of this often devastating illness.

Keywords: schizophrenia, kinome, Signaling network, postmortem, array
Supported by: NIMH

68. Striatal Ablation of Neurogranin Increases Schizophrenia-like Behaviors and Ethanol Drinking

Doo-Sup Choi

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Background: Neurogranin (Ng) is predominantly expressed on the postsynaptic nerve terminal and regulates calcium-calmodulin (Ca2+-CaM) complex binding in response to activation of NMDA and mGluR5 receptors.
Methods: To elucidate the role of Ng, we examined prepulse inhibition, social interaction, ethanol sensitivity, and ethanol-seeking behaviors using Ng KO mice. Then, we employed an AAV-viral mediated gene expression system to investigate Ng dependent behaviors. Using iTRAC proteomics, we examined Ng expression in response to ethanol in the striatum and validated protein expression.
Results: Our results demonstrated that Ng KO mice are deficit in prepulse inhibition and exhibit a social withdrawal phenotype, which are reversed by over-expression Ng in the NAc. Ng KO mice were more sensitive to the acute intoxicating effects of ethanol compared to wild-type, but showed enhanced motivation to seek ethanol and were insensitive to aversion conditioning to ethanol. Interestingly, repeated ethanol exposure in Ng KO mice restored the antisocial behavioral phenotype, which was similar to the effect of Ng overexpression in the NAc, suggesting that ethanol counteracts the loss of Ng. Consistently, ethanol increases Ng expression in the NAc in our iTRAC proteomic analysis along with other glutamatergic signaling molecules.
Conclusions: Our studies indicate that decreased Ng signaling in the NAc promotes ethanol-seeking behaviors and that ethanol reverses antisocial or schizophrenia-like behaviors in Ng KO mice. These findings suggest that Ng is an essential for the comorbidity of schizophrenia-like behaviors and alcohol use disorders.

Keywords: Glutamate, Neurogranin, Alcohol, Schizophrenia, Antisocial
Supported by: R01AA18779

69. EAAT2 and xCT Regulate Alcohol Seeking Behaviors in Rodents

Youssef Sari

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Background: We recently demonstrated that ceftriaxone treatment induced upregulation of glutamate transporter 1 (GLT1) levels as well as attenuated ethanol intake. Objectives. In this study, we investigated the effect of ceftriaxone on the levels of cystine/glutamate exchanger (xCT) in both continuous and relapse-like drinking behaviors, GLT-1 isoforms, and glutamate aspartate transporter (GLAST) in relapse-like ethanol-drinking behavior.
Methods:P rats were exposed to free choice of 15% and 30% ethanol, and water for five weeks, and then deprived from ethanol for two weeks. Rats were treated with ceftriaxone (100 mg/kg, i.p.) or vehicle during the last five days of the two-week deprivation period. A second group of P rats was exposed to similar drinking paradigm for five weeks and then treated with ceftriaxone or vehicle for five days on week six.
Results: We found that ceftriaxone treatment significantly attenuated relapse-like ethanol intake. Importantly, ceftriaxone-mediated attenuation in relapse-like ethanol-drinking behavior was associated in part with upregulation of the levels of GLT-1a and GLT-1b isoforms, and xCT in the PFC and the NAc. We did not observe any significant differences in GLAST expression among all groups, which indicated the specific action of ceftriaxone on xCT and GLT-1 isoforms expression. We also found that ceftriaxone restored xCT levels in both PFC and NAc in continuous ethanol-drinking paradigm.
Conclusions: These findings suggest that xCT and GLT-1 isoforms might be target proteins for the treatment of alcohol dependence.

Keywords: GLT-1, EAAT2, Glutamate, Alcohol Dependence, xCT
Supported by: NIH R01AA019458

70. The Role of Extrasynaptic Glutamate Receptors and Transport Systems in the Regulation of Nucleus Accumbens Basal Glutamate Levels Following Alcohol Self-administration

Lori A. Knacksedt

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Background: Basal extracellular glutamate levels are increased in the nucleus accumbens (NA) core in early withdrawal from alcohol. Glutamate homeostasis in the NA is regulated by multiple mechanisms, including the major glutamate transporter GLT-1. Both extrasynaptic and synaptic glutamate levels are also regulated by Group I and II metabotropic glutamate receptors. Here we examined the contribution of these varied extrasynaptic regulators of glutamate to the elevated levels observed in rats withdrawn from alcohol.
Methods: 65 rats were provided access to unsweetened alcohol (20% v/v) or water for 24 hrs on alternating days for 21 sessions. After 24 hours of withdrawal from the last session, we either conducted microdialysis in the NA core or sacrificed animals to collect NA core tissue for western blotting or slice electrophysiology.
Results: Basal glutamate levels were increased in the NA core of animals which self-administered alcohol; this was accompanied by a significant increase in GLT-1 surface expression. Administration of MTEP, a negative allosteric modulator of mGluR5, decreased glutamate levels only in rats with a history of alcohol consumption, while preventing action potential-dependent release with tetrodotoxin (TTX) did not alter glutamate levels. Electrophysiological recordings indicated that the function of the mGluR2/3 autoreceptors was not altered after alcohol.
Conclusions: This novel data demonstrates that reduced uptake via GLT-1 does not account for increased basal glutamate levels, nor does increased action-potential dependent release or a loss of autoreceptor function. We propose that an mGluR5-dependent mechanism of glutamate release is upregulated in rats with a history of alcohol consumption.

Keywords: glutamate, alcohol, GLT-1, addiction, mGluR5

SYMPOSIUM
Translational Approaches to Stress Neurobiology and Risk for Psychosis in Adolescence: Focus on Gene x Environment Interaction effects on Neural Circuits

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Alberta – Mezzanine
Chair: Aysenil Belger

71. Dysregulation of Stress Systems as a Function of Early Life Adversity: Mechanisms and Possible Consequences for Adolescent Psychopathology

Jens C. Pruessner, Nida Ali, Julie Andrews

Psychiatry, McGill University, Montreal, QC, Canada

Background: Adverse conditions early in life, both during pre- and postnatal periods, have been identified as risk factors for susceptibility for psychopathology during adolescence and adulthood. A change in the sensitivity of the stress systems has been discussed as potential mechanism linking early life stress to later psychopathology.
Methods: In five independent studies including more than 100 healthy individuals, we have investigated the link among variations in perceived early life parental care and the regulation of the cortisol stress system (baseline and in response to stimulation), and the dopamine system, using a combination of stress tests, pharmacological manipulation, and neuroimaging tasks.
Results: All studies demonstrated consistent associations among signs of early life adversity and changes in the cortisol and the dopamine systems. For cortisol, subjects with low early life parental care show signs of changed cortisol awakening response ($p< .01$), afternoon cortisol output (p,.05), and cortisol stress responses ($p=.007$), when compared to subjects with average parental care scores. These changes in cortisol correspond systematically with markers of dopaminergic activity (all $p<.05$).
Conclusions: The available data supports a consistent and significant effect from early life adversity on the regulation of the cortisol and dopamine system. Together, the differential regulation of these systems might present a risk factor for psychopathology in adolescence and adulthood.

Keywords: Stress, Neuroimaging, Early life adversity, Parental bonding, cortisol
Supported by: CIHR

72. Neural Correlates of Social Environmental Risk Factors for Schizophrenia

Heike Tost

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Background: Mental health and social life are intimately interrelated, and prior epidemiological research identified urban upbringing and ethnic minority status as two of the best-established environmental risk factors for schizophrenia. Current explanatory models point to a role for social adversity and altered neural stress processing but the intermediate mechanisms are still underexplored to date.
Methods: The data presented in this talk arise from past and current work of our laboratory on the brain structural and functional correlates of urban upbringing, migration background, and social status in healthy adults. In these studies, brain response to social evaluative stress was studied with functional magnetic resonance imaging (MRI). Associations to regional brain gray matter volumes were examined using structural MRI and voxel-based morphometry.
Results: Our studies provide evidence for an association of urban upbringing and ethnic minority status with elevated neural activity under social stress in the perigenual anterior cingulate cortex (pACC), a key brain region for stress and emotion regulation in humans. Structural findings in the same region point to an adverse interaction of urbanicity and migration background with sex.
Conclusions: Our findings highlight the importance of structural and functional alterations in a neural system for the regulation of negative emotion and stress, raise awareness of the potential somatic implications of social adversity, demonstrate the potential of investigating associations from psychiatric epidemiology using neuroimaging, and encourage future research on the neural convergence mechanisms of genetic and environmental risk factors in this circuitry.

Keywords: social environmental risk factors, schizophrenia, neuroimaging, urban upbringing, ethnic minority status
Supported by: The research leading to these results has received funding from the European Community's Seventh Framework Programme under grant agreement No. HEALTH-F2-2010-241909 (Project EU-GEI)

73. Identifying Gene-environment Interactions in Schizophrenia: Evidence that the Link Between Early Life Stress and Psychosis Is Strong and Evident Across Multiple Psychiatric Disorders

Ruud van Winkel

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Background: Meta-analyses link childhood trauma to depression, mania, anxiety disorders, and psychosis. It is unclear, however, whether these outcomes truly represent distinct disorders following childhood trauma, or that childhood trauma is associated with admixtures of affective, psychotic, anxiety and manic psychopathology throughout life.
Methods: We used data from a representative general population sample (NEMESIS-2; n=6,646), of whom respectively 1,577 and 1,120 had a lifetime diagnosis of mood or anxiety disorder, as well as from a sample of patients with a diagnosis of schizophrenia (GROUP; n=825).
Results: In NEMESIS-2, largely comparable associations were found between childhood trauma and depression, mania, anxiety and psychosis. However, childhood trauma was considerably more strongly associated with their lifetime admixture. These results were confirmed in the patient samples, in which it was consistently found that patients with a history of childhood trauma were more likely to have a combination of multiple symptom domains compared to their non-traumatized counterparts. The presence of co-occurring symptom clusters strongly impacted on correlates of functioning and outcome. In agreement with the non-specificity of the association between childhood trauma and schizophrenia, no evidence for interaction was found between childhood trauma and the schizophrenia PGC2 polygenic risk score in GROUP sample.
Conclusions: Childhood trauma increases the likelihood of admixture of affective, anxiety and psychotic symptoms cutting across traditional diagnostic boundaries, and this admixture is already present in the earliest stages of psychopathology. In the context of childhood trauma, a paradigm shift from traditional psychiatric diagnoses towards cross-diagnostic, etiologically informed phenotypes may be necessary.

Keywords: Childhood Trauma, Stress, Polygenic Risk, Psychosis

74. Adolescent Social Stress and Oxidative Stress in Animal Models

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Background: Oxidative stress and inflammatory processes may play a role in schizophrenia, particularly in early stages. As developmental rodent models provide an opportunity to study neurobiological changes in a brain bound to show behavioral deficits during adolescence, we explored whether rats with a neonatal ventral hippocampal lesion (NVHL) exhibited oxidative stress and whether adolescent antioxidant treatment prevented the emergence of a diverse set of deficits in this model.
Methods: NVHL or sham rats received the redox modulators N-acetyl cysteine (NAC), apocynin or ebselen, or vehicle, from postnatal day (P) 35 to 50. Rats were tested at two age groups: P21, when no behavioral anomalies are yet detected, and P61, when rats are adults and behavioral deficits are evident. We assessed the presence of oxidative stress, parvalbumin levels, and a set of interneuron-dependent physiological and behavioral parameters.
Results: Juvenile and adolescent antioxidant treatment prevented the reduction of prefrontal parvalbumin interneurons observed in the NVHL model, as well as behavioral (prepulse inhibition deficits) and electrophysiological deficits (loss of dopamine modulation of interneuron physiology) present in adult rats with a neonatal hippocampal lesion. Furthermore, NVHL rats exhibited reduced mismatch negativity, and this deficit was prevented by NAC treatment.
Conclusions: Inflammatory responses and oxidative stress could be linked to loss of interneuron function. Targeting inflammatory processes and oxidative stress balance may be a beneficial approach for early intervention and preventive strategies in schizo-

phrenia.

Keywords: schizophrenia, prodrome, animal models, inflammation
Supported by: NARSAD; R01MH57683

SYMPOSIUM
Social Cognition as a New Therapeutic Target in Borderline Personality Disorder: Testing Models, Mechanisms, and Modulators

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Quebec – Mezzanine
Chair: Larry J. Siever*
Co-Chair: M. Mercedes Perez-Rodriguez

***Supported by:** MH56140, MH63875; VA Merit; MIRECC; MO1-RR-00071; CTSA award UL1TR000067

75. Converging Multimodal Evidence for Social Cognitive Abnormalities in Borderline Personality Disorder: Models, Mechanisms and Novel Therapies

M. Mercedes Perez-Rodriguez[1], Antonia S. New[1], Kim E. Goldstein[1], Qiaoping Yuan[2], Zhifeng Zhou[2], Salwa Chowdhury[1], Pei-Hong Shen[2], Ethan Rothstein[1], Liza S. Rimsky[1], Harold W. Koenigsberg[1], Marianne Goodman[1], Colin Hodgkinson[2], David Goldman[2], Erin Hazlett[1], Larry J. Siever[1]

[1]Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, [2]Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD

Background: Although severe interpersonal dysfunction is characteristic of borderline personality disorder (BPD), social cognitive dysfunction has only recently been recognized as a core feature of BPD.
Methods: We examined social cognition abnormalities in BPD using multimodal methodologies, including functional (fMRI) and structural (DTI) neuroimaging, imaging-genetics, genetics, and behavioral paradigms. We examined the effect of dialectical behavioral psychotherapy (DBT) on neuroimaging biomarkers of social information processing in BPD, and tested two untested models of the effect of intranasal oxytocin on social cognition ("interactionist" and "optimizing").
Results: Genetics data in 318 patients with personality disorders (179 with BPD) and 155 healthy controls support the involvement of opioidergic, oxytocinergic, and vasopressinergic systems (critical for normative social cognition and social functioning) in BPD. Understanding of mental states is impaired among veterans (n=78) with BPD and high suicide risk (F=4.7;df=1;p=0.03). Multimodal neuroimaging data suggest abnormalities in emotion processing/social cognition brain networks in BPD. Adolescents with BPD have decreased FA in white matter tracts connecting the amygdala with regions involved in emotion recognition (Wilks F(3,57)=3.55,p<0.02). BPD patients have abnormal amygdala reactivity and a habituation deficit to social stimuli, modulated by BDNF genotypes (F[1,51]=4.48,p<0.04,Wilks). These abnormalities improved after DBT (F(1,20)=4.89;p<0.04). The effect of intranasal oxytocin in BPD will be discussed in relation to the two models described above.
Conclusions: Converging evidence from multimodal data suggest that social cognitive impairment is a core feature of BPD, and that opioids, oxytocin, vasopressin and BDNF modulators are potential molecular targets for development of novel treatments.

Keywords: Borderline Personality Disorder, Social Cognition, Oxytocin, fMRI, BDNF
Supported by: MH56140, MH63875; VA Merit; MIRECC; MO1-RR- 00071; CTSA award UL1TR000067

76. Amygdala and Dorsal Anterior Cingulate Connectivity During Distraction by Interpersonal Pictures in Borderline Personality Disorder Patients with Interpersonal Trauma History

Annegret Krause-Utz[1,2], Bernet Elzinga[2], Nicole Y. L. Oei[3], Christian Paret[4], Inga Niedtfeld[1], Philip Spinhoven[5], Martin Bohus[1], Christian Schmahl[1]

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Background: Working memory is critically involved in ignoring distraction while maintaining goal-directed behavior. Antagonistic interactions between brain regions implicated in emotion processing (e.g. amygdala) and dorsal frontal brain regions involved in cognitive control are assumed to play an important role in coping with emotional distraction. The purpose of the present study was to investigate functional connectivity during an Emotional Working Memory Task in patients with Borderline Personality Disorder (BPD), which is characterized by emotion dysregulation and interpersonal disturbances.
Methods: During functional magnetic resonance imaging, 22 interpersonally traumatized patients with BPD and 22 healthy controls (HC) performed a working memory task, while neutral versus negative interpersonal scenes from the International Affective Picture System were presented. Psychophysiological Interaction (PPI) analysis with bilateral amygdala and dorsal anterior cingulate cortex (dACC) as a-priori defined seed regions of interest was performed. Whole-brain regression analyses with self-reported dissociation were conducted.
Results: During emotional distraction, HC showed negative amygdala connectivity with left dorsolateral prefrontal cortex (PFC), while BPD patients showed a stronger positive coupling of both seeds with right dorsomedial PFC. In addition, patients demonstrated stronger positive amygdala connectivity with bilateral (para)hippocampus and stronger positive dACC connectivity with left posterior cingulate and precuneus during distraction by both neutral and negative interpersonal pictures. Dissociation positively predicted amygdala connectivity with right ACC during emotional distraction in BPD patients (all results Z>3.2, k>10, p<0.001).
Conclusions: These novel findings suggest increased attention to – both normative neutral and negative – task-irrelevant social information, possibly underlying interpersonal disturbances in patients with BPD.

Keywords: Borderline Personality Disorder, emotional distraction, working memory, functional magnetic resonance imaging, Psychophysiological Interaction analysis

77. Neural Correlates of Social and Physical Pain in Borderline Personality Disorder

Melanie Bungert, Magdalena Schumitz, Lisa Liebke, Janine Thome, Christian Schmahl, Martin Bohus, Stefanie Lis

Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany

Background: Social and physical pain serve as an alarm system for the prevention and reaction to physical and mental harm and are assumed to rely on comparable brain structures. Borderline personality disorder (BPD) is characterized by a hyposensitivity to physical pain and a hypersensitivity to social pain. The aim of the present study was to link both pain types to investigate neuronal correlates of social pain and the modulation of physical by social pain in BPD.
Methods: To assess social pain, social exclusion and inclusion were induced with the Cyberball-Paradigm in 30 unmedicated BPD patients and 30 healthy control subjects (HC) in an fmri-block-design. Each cyberball block was followed by either a painful or a non-painful temperature stimulus to assess physical pain.
Results: Enhanced social pain during cyberball in BPD was accompanied by increased insula activation (T=3.87, pSVC-FWE<.05). Social exclusion reduced physical pain sensitivity in both groups, which further accentuated in BPD (F(1,58)=7.62, p=.008). Both groups showed diminished activation in the dACC, the insula and the thalamus (T=3.41, T=4.24, T=3.53; all pSVC-FWE<.05) during pain after exclusion. In contrast to the HCs, BPD patients showed reversed activation patterns in parts of the dACC (T=4.10, p<.001).
Conclusions: Our data confirm previous findings of enhanced sensitivity to social pain also on the neuronal level. Social exclusion led to further accentuation of the known hyposensitivity to physical pain in BPD. Implications for the further understanding of altered social and physical pain processing in BPD will be discussed.

Keywords: Borderline Personality Disorder, social exclusion, social pain, physical pain, fMRI
Supported by: German Research Foundation

78. Oxytocin and Trust in Adolescents with Borderline Personality Disorder

Carla Sharp[1], Amanda Venta[1], Carolyn Ha[1], Elizabeth Newlin[2]

[1]Psychology, University of Houston, Houston, TX, [2]The Adolescent Treatment Program, The Menninger Clinic, Houston, TX

Background: Stanley and Siever (2010) proposed a neuropeptide model of BPD suggesting that dysfunction of oxytocin circuitry impairs social-cognitive function contributing to the interpersonal symptoms of BPD. Oxytocin-related hypotheses have not been examined in adolescent BPD.
Methods: In this ongoing study, we are administering oxytocin vs. placebo to adolescents meeting DSM-5 criteria for BPD (n = 35) and healthy controls (n = 35), with a mean age of 14.62 years (SD = 1.655). Adolescents then play a multiround (i.e., 5 trial) trust game with their mother.
Results: Preliminary results are based on a sample of N = 51 adolescents, 16 of whom met criteria for BPD and 35 of were healthy controls. Of these, 26 were administered an oxytocin nasal spray and 25 were administered a placebo nasal spray. The results of a three-way repeated-measures ANOVA indicated a three way interaction between trial, condition, and BPD status [F (4, 44) = 2.577, p = .050] such that investments increased linearly across trials for healthy controls receiving oxytocin (F = 4.035, p = .063) but not among adolescents with BPD.
Conclusions: While data analyses continue, these results provide preliminary evidence for anomalies in adolescent BPD related to oxytocin responses and lay the foundation for future studies to explore neuropeptide-based models of treatment.

Keywords: oxytocin, social cognition, bordereline personality disorder, adolescents
Supported by: NIMH; American Psychoanalytic Society

SYMPOSIUM
Computational Modeling of Learning and Decision Making in Schizophrenia

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Territories – Mezzanine
Chair: John Krystal
Co-Chair: Andreas Heinz

79. The Link Between Dopamine Dysfunction and Aberrant Learning in Schizophrenia

Anissa Abi-Dargham[1,2], Guillermo Horga[3], Elsmarieke Van de Giessen[3]

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Background: Alterations in dopamine release are observed in schizophrenia and addiction. Since dopamine is involved in learning and adaptive behaviors, one question is whether dopamine alterations are related to aberrant learning within specific functional domains across psychiatric diagnoses.
Methods: We used behavioral tasks to probe reward and sensory processing in patients with schizophrenia, cannabis dependence and matched healthy volunteers. We used [11C]PHNO or [11C] raclopride with the amphetamine paradigm to assess striatal dopamine release. To assess sensory learning, we applied a computational model of predictive coding to fMRI data acquired during an auditory probabilistic discrimination task. We also obtained data using an interval reproduction task (in which duration and variability of a series of pure tones was systematically manipulated) before and after the amphetamine challenge and a weather prediction task to assess learning rate.
Results: Using model-based fMRI, we found deficits in predictive coding in patients with schizophrenia [1]. We also measured a significant relationship between striatal dopamine release and performance on the weather prediction task in cannabis users (associative striatum r = 0.69; n = 8) and in healthy controls (associative striatum r = 0.66; n = 10). Complete analyses of these data sets will be presented.
Conclusions: Alterations in dopaminergic signaling in opposing directions have a dual effect on learning across functional domains by weakening learning from salient or relevant signals and reinforcing stimulus independent signals.

Keywords: Dopamine, Learning, reward, sensory processing, schizophrenia
Supported by: NIMH, NIDA

80. Pavlovian to Instrumental Transfer: Tracking the Transition from Goal-directed to Habitual Behaviour

Philip R. Corlett

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Background: Learning and memory represent key pathophysiological candidates for alcohol dependence. Preclinical models highlight the importance of Pavlovian learning (about environmental predictors of rewards), Instrumental learning (the actions and choices necessary to procure salient outcomes) and their intersection – Pavlovian to Instrumental Transfer (PIT). This intersection demonstrates the powerful impact environmental stimuli might have on decision-making in health and alcoholism.
Methods: In a behavioral task, subjects learned that different visual cues predicted oral delivery of sweet, bitter or neutral solutions (Pavlovian). Subsequently, they learned that button push responses earned the sweet or neutral solutions or avoided the bitter (Instrumental). PIT (transfer) was measured as subjects' response accuracy and reaction time in the presence of the Pavlovian cues. Specific PIT involves an invigoration of a particular response in the presence of the cue that predicted a congruent outcome. General PIT involves the invigoration of all instrumental responses by a salient cue.
Results: Alcohol dependence was associated with less specific PIT. However, dependent subjects showed enhanced general PIT. Dependent subjects responded faster and more accurately in the presence of a cue that reliably predicted a sweet, rewarding outcome, irrespective of whether they were working for sweet, bitter or neutral solution.
Conclusions: General PIT is enhanced by extensive training and habit formation. These data suggest that alcohol dependent subjects have a proclivity toward habit formation compared with goal-directed behavior. These findings will be discussed in the context of the roles of dopamine and glutamate signalling in risk, use and transition to abuse. .

Keywords: Addiction, Alcoholism, Reinforcement Learning, Decision Making, Memory
Supported by: NIAAA:

81. Modelling Reward-related Decision Making and its Functional Correlates in Schizophrenia

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Background: The ability to form predictions about future outcomes relies on neuronal teaching signals, like reward prediction errors (PE) represented in fronto-striatal circuits. Alterations of such basic learning signals have been proposed to contribute to the development of psychotic symptoms in schizophrenia and may be related to dysfunctional dopaminergic neurotransmission. Computational modeling enables quantifying decision making strategies and thus may allow a more detailed description of behavioral and neuronal alterations.
Methods: Schizophrenia patients and healthy controls underwent functional MRI during probabilistic reversal learning and sequential decision making tasks. Detailed computational modeling including model comparison was applied to analyze task strategy and was further utilized for model-based fMRI. In a subsample dopamine synthesis capacity was measured using FDOPA-PET.
Results: Unmedicated schizophrenia patients display reduced behavioral adaptation and reduced goal-directed ('model-based') behavioral control compared to controls. On the neuronal level, reduced striatal PE representation was found compared to controls. Modeling task strategies revealed that a substantial number of psychotic patients showed an idiosyncratic strategy, but a patient subgroup with a similar strategy as controls still revealed reduced striatal representation of informative errors. In healthy controls striatal PE signaling was inversely correlated to presynaptic dopamine synthesis capacity.
Conclusions: Neuronal representation of learning signals are disrupted in schizophrenia patients independent of medication and when accounting for task solving strategy. Our results suggest a relation with presynaptic dopamine which is elevated in schizophrenia patients. Computational modeling can account for differences in cognitive and behavioral strategies and may help to characterize neurobiological informed subgroups.

Keywords: schizophrenia, reversal learning, fMRI, computational modeling, ventral striatum
Supported by: German Research Foundation, Max Planck Society

82. The Structure of Movement Patterns as Predictor of Schizophrenia Symptom Dimensions

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Background: Real life behavior such as spontaneous motor activity can be linked to schizophrenia symptoms, such as avolition. The more complex behavioral symptom 'disorganization' refers to action planning and goal directed behavior. We hypothesized that disorganization would be reflected by irregular movement patterns. Therefore, we analyzed the temporal structure of spontaneous motor behavior to test whether it was predictive for disorganization.
Methods: We applied time series analyses to wrist actigraphy data of 100 schizophrenia patients. Spontaneous movements were recorded in 2s intervals for 24 hours. Data from 2 defined 60-min periods were analyzed, and partial autocorrelations of the actigraphy time series indicated predictability of movements in each individual. The number of time lags with sufficient partial autocorrelation was used as marker of temporal stability. Patients were assessed with the Positive And Negative Syndrome Scale.
Results: Each of the syndrome scores for disorganization and positive symptoms were predicted by instable movement patterns ($p<0.05$), but not by the quantitative amount of movement. Negative symptoms, on the other hand, were unrelated to the qualitative movement pattern, but influenced by the amount of movement ($p<0.05$). The type and dosage of current antipsychotic medication was unrelated to the stability of movement patterns.
Conclusions: The temporal stability of objectively measured movement patterns is meaningful for the disorganization dimension in schizophrenia. Particularly, irregular spontaneous movements predicted ratings of disorganization, indicating disturbances in goal directed behavior. The findings have implications for translational research. The neurophysiological correlates of the stability of

spontaneous movement patterns will be further investigated.

Keywords: Disorganization, Actigraphy, Time Series Analyses, Negative Symptoms

SYMPOSIUM
New Findings and Future Outlooks from Studies of Biomarkers for Precision Medicine in Affective Disorders (MDD and Mania)

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Tudor 7 – Main Mezzanine
Chair: Martijn Arns
Co-Chair: Gerard Bruder

83. Pre-treatment Brain MRI Measures to Identify Individuals Who Will and Will Not Remit During Acute Phase Treatment With Anti-depressant Medications – Results From the iSPOT-D Study

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Background: Antidepressant medications (ADMs) form the front-line treatment for major depressive disorder (MDD). Yet less than 50% of patients reach symptomatic remission with their first treatment. Clinically useful objective measures to reliably predict which individuals will achieve remission to ADMs are yet to be established.
Methods: 157 MDD participants underwent baseline MRIs and completed eight weeks of treatment with escitalopram, sertraline or venlafaxine-XR as part of the iSPOT-D study. A score at week 8 of 7 or less on the 17 item Hamilton Rating Scale for Depression defined remission. Receiver Operator Characteristics (ROC) analysis using the first 50% participants were performed to identify the best possible combination of pre-treatment measures and cut-points to define decision trees that prospectively predict remission status. These decision trees were tested for replication in the remaining participants.
Results: Overall, 35% of all participants achieved remission. ROC analyses identified two decision trees that predicted a high probability of non-remission and that were replicated: 1. Left middle frontal volume less than 14.3mL & right angular gyrus greater than 6·3mL identified 55% of non-remitters with 85% accuracy; and 2. Fractional anisotropy values in the left cingulum bundle<0·63, right superior fronto-occipital fasciculus<0·54 and right superior longitudinal fasciculus<0·50 identified 15% of the non-remitters with 84% accuracy.
Conclusions: The findings contribute new knowledge about objective neuroimaging measures for identifying a large proportion of non-remitters before treatment begins, going beyond the current knowledge on clinical predictors of non-remission. Findings are consistent with a neuroanatomical basis for non-remission in depressed patients.

Keywords: Magnetic resonance imaging, biomarkers, prediction, major depressive disoders, iSPOT-D
Supported by: Brain Resource Ltd

84. First EEG Results of the iSPOT Study in Depression: EEG Alpha Asymmetry as a Gender Specific Predictor of Treatment Outcome to Sertraline And Escitalopram

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Background: Measures of alpha and theta electroencephalogram (EEG) activity often differentiate patients with major depressive disorder (MDD) from normal controls, and some evidence suggests these measures relate to overall antidepressant response. This study aimed to determine whether these measures would distinguish MDD patients from controls, whether these measures behave as overall and differential predictors of outcome to three antidepressants and to explore the effects of gender.
Methods: In the international Study to Predict Optimized Treatment Response in Depression (iSPOT-D), a multi-center, international, randomized, prospective open-label trial, 1008 MDD patients were randomized to Escitalopram, Sertraline or Venlafaxine-XR and 336 controls were assessed. Treatment response was established after eight weeks and resting state EEG was assessed at baseline.
Results: No differences in alpha for occipital and frontal cortex and alpha asymmetry were found between MDD and controls. Alpha in occipital and frontal cortex were not associated with treatment outcome. However, a gender and drug-class interaction effect was found for frontal alpha asymmetry ($p<.001$). Relatively greater right frontal alpha in women only was associated with response (ES=0.44) and remission (ES=0.55) to the SSRI Escitalopram and Sertraline but not the SNRI Venlafaxine-XR. Furthermore, decreased theta in frontal cortex and rACC was associated with response to all 3 drugs.
Conclusions: In women only, pretreatment alpha-asymmetry predicted response and remission to Escitalopram and Sertraline, but not to Venlafaxine-XR. Future studies should separately analyze effects in EEG alpha power for men and women and elucidate the

nature of the gender and drug specific effects of alpha asymmetry.

Keywords: Depression, Precision Medicine, QEEG, Alpha, Theta
Supported by: Vrain Resource Ltd. (Sydney, Australia)

85. EEG-Based Assessment of Brain-Arousal Regulation (Research Domain Criterion): Relevance for Affective Disorders and ADHD

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Background: According to a recently presented concept the hyperactivity and sensation seeking observed in overtired children, ADHD and mania have to be interpreted as autoregulatory attempts of the organism to stabilize vigilance ("Brain-arousal") by increasing external stimulation. Correspondingly the withdrawal and sensation avoidance in major depression (MD) is interpreted as a reaction to a state of tonically high vigilance. Vigilance regulation is a converging biomarker which can be objectively assessed with a recently developed EEG-based algorithm (Vigilance Algorithm Leipzig, VIGALL).Studies on its physiological, diagnostic and predictive validity will presented.
Methods: Physiological validity: GWAS + candidate gene analyses concerning vigilance regulation (n = 820). Changes of vigilance regulation during therapeutic sleep deprivation in MD (n=18) and healthy controls (n=18).
Diagnostic validity: vigilance regulation in unmedicated (n=40) and medicated (n=61) patients with MD compared to healthy controls, to patients with bipolar disorder studied both during mania (n = 17) and depression (n=19), and to adult ADHD (n=80).
Predictive validity: vigilance regulation in responders and nonresponders to treatment with antidepressants (n = 71).
Results: Vigilance regulation is hyperstable in MD compared to healthy controls and normalizes with improvement of depression. In bipolar patients an unstable vigilance regulation with rapid declines to drowsiness or sleep states is observed during mania and the opposite during depression.
Conclusions: Vigilance regulation as assessed with the VIGALL is a state modulated trait and a valid biomarker for assessing brain-arousal regulation. This biomarker has also diagnostic and predictive validity making it promising for clinical and research purposes.

Keywords: mania, depression, EEG, ADHD, arousal

86. Electrophysiological and Neurocogitive Predictors of Clinical Response to Antidepressants and Cognitive Behavioral Therapy for Depression

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Background: There is growing evidence that electrophysiological (EEG and evoked or event-related potentials) and neurocognitive tests have value as markers for predicting antidepressant response. We present findings for several studies using: (1) resting EEG in the alpha band; (2) loudness dependence of auditory evoked potentials (LDAEP); and (3) neurocognitive tests.
Methods: These measures are being used in a multi-site project "EMBARC_Establishing Moderators and Mediators of Antidepressant Response for Clinical Care", in which 400 depressed patients are randomized double-blind to 8 weeks of treatment with a SSRI or placebo, with nonresponders switched to a SSRI or NDRI, and in 40 healthy adults for evaluating the test-retest reliability. In separate studies, depressed patients were tested before 12 weeks of treatment with a SSRI, NDRI or combined treatments, or 14 weeks of cognitive behavioral therapy (CBT).
Results: High test-retest reliability was found for EEG alpha (r=.89), N1 dipole during LDAEP (r=.87) and neurocognitive tests of word fluency (r=.81) and RT (r≥.90). Responders to serotonergic antidepressants differed from nonresponders on these tests, with relatively high specificity (.70-.92), but lower sensitivity (.50-.69). Resting EEG alpha and neurocognitive tests did not predict response to CBT, but as in a prior study, greater left hemisphere advantage for dichotic words predicted response to CBT, with relatively high sensitivity (.73) and specificity (.89).
Conclusions: Electrophysiological and neurocognitive tests are reliable and have potential as predictors of response to treatments for depression. The EMBARC project will evaluate whether combining them with clinical and neuroimaging measures further improves differential prediction.

Keywords: Depression, Electrophysiology, Neurocognitive, Antidepressants, Biomarkers
Supported by: NIMH grants U01MH092250 and R01MH36295

SYMPOSIUM
Understanding Fear Circuits to Identify Effective Treatments

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Canadian – Convention Floor
Chair: Raül Andero

87. Understanding Fear Memory Encoding Is Critical for Improving Memory Strength

Gleb Shumyatsky[1], Shusaku Uchida[2], Guillaume Martel[3]

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Background: Changes at synapses and in the nucleus are critical for memory, but remain unclear. We followed synaptosomal microtubules and CREB-mediated gene transcription to understand dynamic processes occurring at the synaptic sites and the nucleus during fear learning.
Methods: We used transgenic/knockout mice and AAV-viral injections as well as synaptosomal fractionation, co-immunoprecipitation and ChiP assay to examine protein interactions following fear conditioning and the effect of these interactions on long-term memory.
Results: Microtubule dynamics regulate many biological processes, but their role in memory remains unclear. We show that learning causes biphasic changes in stathmin microtubule-destabilizing activity as well as microtubule stability. Changes in microtubule stability affect microtubule-mediated localization of the GluA2 subunit of AMPA receptors at synaptic sites. An increase in microtubule stability by the drug paclitaxel increases memory. Both stathmin mutant mice and aged wild-type mice display deficits

in stathmin activity, microtubule stability, GluA2 localization and memory, and blocking GluA2 endocytosis rescues the memory deficits. Thus, microtubule dynamics at synapses are critical for memory encoding. Although increasing evidence implicates epigenetic control of gene transcription in memory formation, it remains unclear how synaptic signals are relayed to the nucleus and induce chromatin modifications and the subsequent transcription of genes required for memory formation. We find that learning-dependent translocation from synapses to the nucleus of the CREB-regulated transcriptional co-activator (CRTC1) regulates CREB-mediated gene transcription of its gene targets.
Conclusions: Learning-dependent dendritic transport linking dynamic changes at the synaptic sites and in the nucleus are critical targets for improving memory.

Keywords: learning-dependent, synapse, nucleus, dendritic transport, microtubules
Supported by: R01MH080328; Whitehall Foundation

88. HPA Axis Suppression and FKBP5 Regulation in Enhancing Fear Extinction: A Mouse Model of PTSD

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Background: Posttraumatic stress disorder (PTSD) occurs in some individuals exposed to traumatic situations and is among the most prevalent and debilitating anxiety disorders with altered fear learning. Improvements in current treatments are needed to decrease the prevalence of PTSD. The FKBP5 gene is involved in modulating activity of the hypothalamic-pituitary-adrenal (HPA) axis during stress responses and it is associated with PTSD. We have previously shown that mice stressed by immobilization to a wooden board (IMO) present impaired fear extinction, which is a key component of PTSD.
Methods: A Half of the mice were exposed to a single IMO. Six days later all mice were tested for cued-fear acquisition and extinction. HPA axis activity was evaluated by measuring corticosterone levels after behavior. Dexamethasone was given i.p. to suppress the HPA-axis stress response during fear acquisition. Following fear extinction we measured Fkbp5 mRNA levels in the amygdala, as well as DNA methylation of the Fkbp5 gene.
Results: Animals previously exposed to IMO had impaired fear extinction and ($p<.001$) increased levels of corticosterone after both cued-fear acquisition and extinction ($p<.01$). Additionally, dexamethasone enhanced fear extinction and decreased Fkbp5 mRNA levels in the amygdala ($p<.05$). Concordantly, preliminary data suggest that Fkbp5 methylation levels were increased in the CpG4 island.
Conclusions: The data suggest that the enhancement of fear extinction with dexamethasone is associated with genomic changes within the Fkbp5 gene. Dexamethasone is a safe and well tolerated drug in humans. Thus, making dexamethasone-suppression of HPA function a promising approach for the treatment of PTSD.

Keywords: PTSD, Fear, Amygdala, FKBP5, HPA
Supported by: 1R21MH101492-01

89. Targeting Fear and Avoidance Circuits with Deep Brain Stimulation

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Background: Deep brain stimulation (DBS) of ventral capsule/ventral striatum (VC/VS) reduces anxiety and compulsive symptoms in refractory Obsessive-Compulsive Disorder (OCD). In rodents, DBS of VS reduces the expression of conditioned fear, enhances its extinction, and induces plasticity in cortico-amygdala circuitry. Patients suffering from harm-avoidant OCD believe compulsions protect them from danger. Therefore, compulsions can be viewed as persistent avoidance responses. OCD is treated with exposure-with-response-prevention (ERP) therapy, where patients are exposed to trigger stimuli but prevented from expressing compulsions in order to extinguish avoidance responses.
Methods: We developed an extinction-with-response-prevention ("Ext-RP") task in rats. Rats are trained to avoid a tone-signaled shock by stepping onto a nearby platform. After training, rats are given 3 days of extinction training with access to the platform blocked with a Plexiglas barrier (resembling ERP). The following day, the barrier is removed to test for avoidance. Rats showing persistent avoidance undergo DBS of VS during an additional "Ext-RP" session. In a separate experiment, the lateral orbitofrontal cortex (lOFC) is pharmacologically inactivated during the avoidance test.
Results: Following "Ext-RP" training, 25% of rats persisted in avoidance ($n=15/59$). During an additional "Ext-RP" session, DBS of VS abolished persistent avoidance ($n=14$, $p<0.01$), without reducing freezing. Inactivation of lOFC also reduced persistent avoidance ($n=12$, $p<0.01$).
Conclusions: Our findings suggest that "Ext-RP" task in rats may be a useful model to characterize neural mechanisms impaired in OCD. DBS enhancement of "Ext-RP" resembles DBS enhancement of ERP in the clinic, and may act by reducing lOFC activity that drives persistent avoidance.

Keywords: fear extinction, obsessive compulsive disorder, exposure with response prevention, ventral striatum, orbitofrontal cortex
Supported by: P50MH086400, R37MH058883, R36MH105039

90. Translational Approaches to Fear Processing in Posttraumatic Stress Disorder

Kerry Ressler[1], Raul Andero[2], Paul Marvar[3], Maria Nylocks[4]

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Background: We review translational approaches to PTSD, from bottom-up and from top-down discovery approaches, with new data on the role of Tachykinin2 (Tac2) in the centromedial amygdala (CeM) and Angiotensin 1a (At1a) expressed broadly, particularly within amygdala.
Methods: We use discovery approaches with RNA profiling in

rodent models of dysregulated fear and human observational studies. Follow-up analyses include pharmacological and targeted genetic approaches in mice and human genetic physiological, and phenotype analyses in highly traumatized human populations.
Results: The Tac2 gene product, NkB, and its receptor, Nk3R, are involved in consolidation of fear memories. Increased Tac2, through a stress-induced PTSD-like model, or following lentiviral overexpression, both enhance fear consolidation, which is blocked by the Nk3R antagonist, osanetant, which is safe in humans. Also, silencing of Tac2-expressing neurons in CeA with DREADDs impairs fear consolidation.
In humans, a significant association was found with presence of an At1a blocker and decreased PTSD symptoms (PSS, 11.4 vs 14.9, p=.01) and in followup studies (N=776). Furthermore, the rs4311 SNP within the ACE gene, implicated in panic attacks, also associates with PTSD (N=3803). The rs4311 genotype modified the effect of ACE-Is or ARBs on PTSD symptoms (N=443; F1,443=4.41, p<0.05). Mouse pharmacogenetic enhancement of extinction by losartan (p<0.05) will also be presented.
Conclusions: These data support bench-to-bedside and reverse translational approaches in understanding fear regulation and translationally-informed treatments for PTSD. Together they provide a new understanding of Tac2 and At1R within amygdala in fear processing and may provide novel approaches to intervention for fear-related disorders.

Keywords: PTSD, Tachykinin, Angiotensin, Fear, Therapy
Supported by: R21MH101492; R01MH096764; P51OD011132

SYMPOSIUM
(Epi)-Genetic Regulation of Resiliency to Traumatic Stress

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Ontario – Convention Floor
Chair: Eric Vermetten
Co-Chair: Dewleen G. Baker

91. Genomic Predictors of Combat Stress Vulnerability in U.S. Marines: Genome-wide Association Studies Across Multiple Ancestries Identify Novel Risk Factors for PTSD

Caroline Nievergelt[1,2], Adam Maihofer[1], Victoria Risbrough[1,2], Dewleen Baker[1,2]

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Background: Genetic association studies on posttraumatic stress disorder (PTSD) have just begun to be performed at the genome-wide level. We present a GWAS from the Marine Resiliency Study (MRS), a prospective longitudinal study on PTSD risk/resilience in combat-exposed Marines. PTSD risk loci from the literature and polygenic risk scores across psychiatric disorders were also evaluated.
Methods: Unrelated, trauma-exposed males (N=3,494) were assessed on the Clinician-Administered PTSD Scale (CAPS); 940 were diagnosed as PTSD cases. Individual genetic ancestry was determined by supervised cluster analysis for subjects of European, African, Hispanic/Native American, and other descent. DNA was genotyped on the HumanOmniExpressExome array. To test for association of SNPs with PTSD, logistic regressions were performed within each ancestry group and results were combined in meta-analyses. Polygenic risk scores from the Psychiatric Genomic Consortium were used for major depressive disorder (MDD), bipolar disorder (BPD), and schizophrenia (SCZ).
Results: The GWAS meta-analysis identified the phosphoribosyl transferase domain containing 1 gene (PRTFDC1) as a genome-wide significant PTSD locus (rs6482463; OR=1.47, SE = 0.06, p=2.04x10-9). Loci with suggestive evidence of association (n=25 genes, p<5x10-6) further implicated genes related to immune response and the ubiquitin system. A cross-disorder analysis of polygenic risk scores from GWASs found that PTSD diagnosis was associated with risk sores of BPD, but not with MDD or SCZ.
Conclusions: Our findings indicate that the genetic architecture of PTSD may be determined by many SNPs with small effects, and overlap with other neuropsychiatric disorders, consistent with current findings from large GWAS of other psychiatric disorders.

Keywords: PTSD, GWAS, Ancestry, cross-disorder, combat stress
Supported by: R01 MH093500

92. Blood-based DNA Methylation Signatures of Susceptibility to Traumatic Stress; Results From A Dutch Prospective Military Cohort Study

Bart Rutten[1], Eric Vermetten[2], Christiaan Vinkers[3], Ehsan Pishva[4], Gunter Kenis[1], Laurence de Nijs[1], Lars Eijssen[5], Wolfgang Viechtbauer[1], Daniel van den Hove[6], Karla Schraut[6], Klaus-Peter Lesch[6], Nikolaos Daskalakis[7], Rachel Yehuda[7], Leonard Schalkwyk[8], Katie Lunnon[9], Jonathan Mill[9], Caroline Nievergelt[10], Dewleen S. Baker[10], Elbert Geuze[11], Marco P. M. Boks[11]

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Background: Traumatic stressors are important risk factors for psychiatric disorders, but people differ strikingly in their susceptibility to develop signs and symptoms of mental illness after traumatic stress. Recent studies suggest that DNA methylation could represent a prime molecular candidate mechanism regulat-

ing inter-individual differences in susceptibility to traumatic stress exposure.
Methods: Our primary analyses were carried out on 96 male soldiers from an existing longitudinal Dutch military cohort assessed before and 6 months after deployment to Afghanistan. Combat trauma exposure and PTSD symptoms were measured using validated questionnaires. Methylome-wide analyses of DNA methylation profiles were performed using Illumina's 450K methylation arrays.
Results: Genome-wide significant associations between longitudinal changes in methylation profiles and longitudinal alterations in PTSD symptom scores were observed for 17 loci from a total of 10 genes in trauma-exposed subjects. Mediation analyses indicated that the strength of the associations between trauma and PTSD symptom development co-depended on methylation at these loci. Blood-brain correlation analyses (using available data from another sample) on the genome-wide significant loci showed strong and statistically significant correlations between the methylation profiles in blood and those in brain. Evidence for replication for several of these 17 loci was observed in an independent longitudinal military cohort (i.e. the Marine Resiliency Study). Further, mRNA expression analyses of the identified genes in blood samples of male animals of the rodent predator scent stress model provided evidence for cross-species validation.
Conclusions: These findings suggest that DNA methylation mediates the effects of combat trauma exposure on PTSD development.

Keywords: Epigenetics, PTSD, DNA methylation, epidemiology, gene expression
Supported by: NWO, Veni Award 916.11.086 to BPFR

93. Longitudinal Changes of Telomere Length and Epigenetic Age Related to Traumatic Stress and Post-traumatic Stress Disorder

Marco P. M. Boks[1], Hans van Mierlo[1], Bart P. F. Rutten[2], Timothy R. D. J. Radstake[3], Lot D. De Witte[1], Elbert Geuze[4], Steve Horvath[5], Leonard C. Schalkwyk[6], Christiaan H. Vinkers[1], Jasper C. A. Broen[3], Eric Vermetten[7]

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Background : Several studies have reported an association between traumatic stress and telomere length suggesting that traumatic stress has an impact on aging at the cellular level. A newly derived tool provides an additional means to investigate cellular aging by estimating epigenetic age based on DNA methylation profiles.
Methods: From an existing longitudinal cohort study, 96 male soldiers were selected based on trauma exposure and the presence of symptoms of PTSD. All military personnel were deployed in Afghanistan and assessed before and 6 months after deployment. In DNA from whole blood telomere length was measured and DNA methylation levels were assessed using the Illumina 450K DNA methylation arrays. Epigenetic aging was estimated using the DNAm age estimator procedure.
Results: The association of trauma with telomere length was in the expected direction but not significant (B=-10.2, p=0.52). However, contrary to our expectations, development of PTSD symptoms was associated with the reverse process, telomere lengthening (B=1.91, p= 0.018). In concordance, trauma significantly accelerated epigenetic aging (B=1.97, p=0.032) and similar to the findings in telomeres, development of PTSD symptoms was inversely associated with epigenetic aging (B=-0.10, p= 0.044). Blood cell count, medication and premorbid early life trauma exposure did not confound the results.
Conclusions: Overall, in this longitudinal study of military personnel deployed to Afghanistan we show an acceleration of ageing by trauma. However, development of PTSD symptoms was associated with telomere lengthening and reversed epigenetic aging. These findings warrant further study of a perhaps dysfunctional compensatory cellular aging reversal in PTSD.

Keywords: PTSD, Epigenetics, Aging, Tellomeres, Biomarker

94. Gene Expression Profiling in Blood as a Predictor of Brain Susceptibility Pathways to Traumatic Stress

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Background: Delineating the molecular basis of individual differences in the stress response is critical to understanding the pathophysiology and treatment of posttraumatic stress disorder (PTSD).
Methods: In this study, 7 d after predator-scent-stress (PSS) exposure, male and female rats were classified into vulnerable (i.e., "PTSD-like") and resilient (i.e., minimally affected) phenotypes on the basis of their performance on a variety of behavioral measures. Genome-wide expression profiling in blood and three brain regions involved in stress regulation (amygdala, hippocampus and prefrontal cortex), followed by quantitative PCR validation, was performed in these two groups of animals, as well as in an unexposed control group.
Results: Differentially expressed genes were identified in blood and brain associated with PSS-exposure and with distinct behavioral profiles postexposure. There was a small but significant between-tissue overlap for the genes associated with exposure-related individual differences, indicating convergent gene expression in both sexes. To uncover convergent signaling across tissue and sex, activated/deactivated transcription factors and pathways were predicted and weighted gene co-expression network analysis was conducted. Glucocorticoid-related signaling was the most con-

vergent pathway associated with individual differences. Targeting this pathway before or after PSS-exposure prevented or rescued anxiety and hyperarousal, respectively.
Conclusions: In conclusion, genes, pathways and gene networks associated with extreme differences in the traumatic stress behavioral response can be distinguished from those associated with trauma exposure. Blood-based biomarkers can predict aspects of brain signaling. Glucocorticoid-related signaling is a convergent pathway associated with trauma-related individual differences in both sexes, and can be the basis of prevention and treatment strategies for PTSD.

Keywords: predator stress, transcription regulation, glucocorticoids, treatment, PTSD
Supported by: Department of Defense Grant W81XWH-08-2-0021; United States Army Medical Research and Materiel Command W81XWH-13-1-0071

SYMPOSIUM
Psychiatric Neuromodulation: Bridging Mechanisms to Therapeutics

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Manitoba – Mezzanine
Chair: Noah S. Philip*

***Supported by:** VA CSR&D, 1IK2CX000724

95. What Goes Up, Can Come Down: Interleaved TMS/bold Imaging Reveals that Medial Prefrontal Cortex Stimulation Can Modulate Nucleus Accumbens Activity in Substance Dependent Individuals

Colleen A. Hanlon

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Background: Vulnerability to drug related cues is one of the leading causes for continued use and relapse among substance dependent individuals. Using drugs in the face of cues may be associated with dysfunction in at least 2 neural circuits: 1) elevated activity in frontal-striatal circuits that govern limbic arousal (including the MPFC and ventral striatum) or 2) depressed activity in frontal-striatal circuits that govern cognitive control (including the DLPFC and dorsal striatum).
Methods: Transcranial magnetic stimulation (TMS) is emerging as a promising new tool for the attenuation of craving among multiple substance dependent populations. To date however nearly all rTMS studies in addiction have focused on amplifying activity in frontal-striatal circuits that govern cognitive control.
Results: This presentation will review recent work using TMS as a tool to decrease craving for multiple substances, provide a theoretical model for how clinical researchers might approach target and frequency selection for TMS of addiction, and presents recent data suggesting that attenuating MPFC activity through cTBS directly decreases craving and activity in the monosynaptic projection areas of the ventral striatum.
Conclusions: The pilot data from this single-blind, sham-controlled, crossover study in cocaine-dependent individuals suggest that, while many TMS studies are focused on applying LTP-like stimulation to the DLPFC, the MPFC might be a new, efficacious, and treatable target for craving in substance dependent populations.

Keywords: addiction, brain stimulation, neuroimaging, craving, connectivity
Supported by: K01DA027756, R01DA036617, P50 DA015369

96. Can We Use Brain Oscillations to Guide Treatment of MDD?

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Background: Brain networks show increased functional connectivity in MDD, marked by highly synchronous rhythmic oscillations on quantitative electroencephalography (qEEG). We examined whether modulating oscillations would be an effective treatment, and whether early changes in oscillations during treatment would predict remission of depression.
Methods: In the first study, we examined whether modulation of

the alpha (8-12 Hz) rhythm would improve symptoms in MDD. 120 subjects with moderate MDD were treated in a six-week double-blind sham controlled trial of a novel device to modulate brain oscillations. The device used rotating neodymium magnets to impart subthreshold sinusoidal waveform transcranial magnetic stimulation synchronized to an individual's alpha frequency, termed synchronized TMS (sTMS). In the second study, we examined whether early shifts in alpha and theta (4-8 Hz) oscillations predict remission during medication or placebo treatment. qEEG was performed before and after one week of treatment in initial (N = 70) and replication (N = 76) cohorts treated with escitalopram or with placebo (N = 48).
Results: Subjects treated with sTMS had significantly greater decrease in HamD17 scores than those treated with sham (-9.00 versus -6.56, p = 0.033), with the largest difference seen in treatment resistant subjects (-8.58 vs. -4.25, p = 0.017). During medication treatment, subjects with a shift in oscillations from the theta to alpha band had 5.2-29.3 greater odds of remission. There was no significant relationship between shifts in oscillations and outcome of placebo treatment.
Conclusions: These results suggest that modulation of oscillations may contribute to effectiveness of both TMS and medication treatment for MDD.

Keywords: synchronized transcranial magnetic stimulation, theta and alpha oscillations, randomized control trial, quantitative electroencephalography (qEEG), thalamocorticol oscillators
Supported by: NeoSync, NCCAM R01AT002479, NIMH R01MH085925, Eli Lily and Co; Wyeth (PFizer); Aspect Medical Systems (Covidien)

97. Low Field Magnetic Stimulation in the Treatment of Depression

Michael L. Rohan

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Background: LFMS is a potential new treatment for depression that uses a low field, high frequency stimulation to produce immediate improvement in mood. Recently we have shown these effects in populations of subjects with Bipolar Disorder as well as with Major Depressive Disorder. LFMS relies on electric fields in the brain that have strengths of less than 1 V/m, delivered at 1kHz. An additional differentiation of LFMS from other modalities is that it is administered globally, rather than locally.
Methods: In following the mechanism of treatment from fields to feelings we have characterized the electromagnetic field penetration of LFMS in closed form models as well as in Finite Element Method. Closed form solutions used a sphere model to allow analysis with harmonic functions, and thus enable characterization of the dependence of the field distribution in the head on model parameters. FEM calculations were performed using an MRI model of a head to obtain in vivo electric field solutions.
Results: Electric fields were found to penetrate throughout the cortex and to have a strong radial dependence.
Conclusions: This implies that LFMS interacts with the brain in cortical regions, and we suggest that prefrontal regions involved in mood regulation experience the primary physiological effects of LFMS treatment.

Keywords: Electromagnetic Stimulation, Depression, Electromagnetic Fields, Bipolar Disorder
Supported by: Stanley Medical Research Institute, Depressive and Bipolar Disorders Alternative Treatment Foundation

98. State-Dependent Modulation of Cortical Oscillations by Non-Invasive Brain Stimulation

Flavio Frohlich

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Background: Transcranial Current Stimulation (TCS) modulates cortical network activity patterns. Yet, little is known about the interaction between stimulation and endogenous brain dynamics that is required for effective targeting of stimulation. Models predict that enhancement of oscillations requires matching the stimulation frequency to the endogenous oscillation frequency.
Methods: To test this hypothesis, we combined optogenetic activation of cortical networks with electric field stimulation in vitro.
Results: Only the endogenous oscillation was enhanced, even for mismatched stimulation frequency ($p<0.001$). In contrast, in absence of optogenetically-induced oscillations, electric field stimulation enhanced activity at all stimulation frequencies ($p<0.001$). We validated this state-dependent effect by 10Hz stimulation of a patient with implanted subdural recording electrodes (eyes closed: pronounced alpha oscillation; cognitive task: suppressed alpha oscillations). The simultaneous recordings showed similar state-dependent modulation of oscillation frequency where during eyes closed the stimulation enhanced the endogenous oscillation ($p<0.001$) whereas during the cognitive task the oscillation frequency was shifted to the stimulation frequency ($p<0.001$, $d=0.033$).
Conclusions: Together, these data support the presence of state-dependent responses to periodic brain stimulation. Therefore, our work offers (1) a new perspective on the rational choice of stimulation parameters for modulation of cortical oscillations as a function of endogenous activity and (2) demonstrates the successful integration of computer simulations, animal models, and human studies for elucidating the dynamic interaction between brain stimulation and endogenous network dynamics. This approach will facilitate the development of individualized and adaptive brain stimulation treatments for psychiatric illnesses with pathological cortical oscillations such as schizophrenia, depression, and autism.

Keywords: tACS, brain stimulation, cortex, neurophysiology
Supported by: R01 MH101547

SYMPOSIUM
Trans-Diagnostic Neurocognitive Traits: Realizing Dimensional Psychiatry
Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Confederation 3 – Mezzanine
Chair: Claire M. GIllan*

***Supported by:** Wellcome Trust 101521/Z/12/Z

99. Model-based and Model-free Learning: A Trans-diagnostic Approach

Valerie Voon

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Background: Impairments in reinforcement learning have been shown to underlie a range of psychiatric disorders from disorders of addiction, schizophrenia to obsessive compulsive disorder. Here we assess goal-directed and habitual learning modeled using computationally based reinforcement learning algorithms as model-based and model-free learning across disorders of compulsivity. We also investigate the influence of motivational states and valence on these processes.
Methods: We use a two-step task to assess model-based and model-free learning across disorders of compulsivity. We assess grey matter volume and intrinsic neural correlates of these two systems using voxel-based morphometry and multi-echo resting state functional MRI. We further modified outcome and motivation using monetary loss and food restriction.
Results: We show a shift away from goal-directed towards habitual behaviours in abstinent methamphetamine users, obese subjects with binge eating disorder and obsessive compulsive disorders (OCD). Abstinence from alcohol was associated with a decrease in habitual behaviours. OCD compulsive severity correlated with enhanced habitual behaviours to reward. Model-based goal-directed learning was correlated with greater medial orbitofrontal volume and greater connectivity between medial orbitofrontal and ventral striatum whereas model-free habit learning was correlated with greater connectivity between supplementary motor area and posterior putamen. We further show an influence of motivation: negative valence enhances goal-directed behaviours in OCD and hunger and shifts in food value influences model-free learning towards food.
Conclusions: Our findings emphasize a trans-diagnostic approach towards model-based and model-free learning and highlights the influence of motivation.

Keywords: addiction, obsessive compulsive disorder, goal-directed learning, habit learning, motivation
Supported by: Wellcome Trust 093705/Z/10/Z

100. Reinforcement Learning Markers of Variation in Compulsive and Depressive Traits

Claire M. Gillan[1], Michal Kosinski[2], Elizabeth A. Phelps[3], Nathaniel D. Daw[4]

[1]New York University, [2]Computer Science Department, Stanford University, Stanford, CA, [3]Department of Psychology, New York University, New York, NY, [4]Center for Neural Science, New York University, New York, NY

Background: Identifying neurocognitive markers of psychiatric disorders is methodologically fraught due to the high rate of shared heritability and co-morbidity across disorders. To remedy this, the present study assessed the relationship between normal variation in psychiatric symptoms (obsessive-compulsive disorder (OCD), depression, anxiety) and previously established neurocognitive features of the former two disorders (goal-directed learning and reward sensitivity).
Methods: 580 subjects were tested online using a reinforcement-learning task previously shown to dissociate goal-directed (model-based) learning from reward sensitivity (model-free). Participants completed questionnaires assessing obsessive-compulsive, depressive and anxious traits, in addition to an IQ test. Data were analyzed using a mixed effects linear regression model where clinical scale total scores were fixed effect predictors.
Results: Normal variation in OCD-symptoms was predictive of deficits in trial-by-trial goal-directed control over action. This relationship was highly specific, such that depression and anxiety symptoms did not contribute to this effect. Depression was associated with a reduction in the contribution model-free learning signals to choice behavior, such that depressives' stay/shift responses were less sensitive to reward. Notably their model-based learning was intact, suggesting that their impairments in reward sensitivity are selective.
Conclusions: Utilizing a large sample, these data indicate that goal-directed learning and reward sensitivity are dimensional traits associated with normal variation in obsessive-compulsive and depressive features respectively. There was no relationship between trait anxiety and either of these neurocognitive features. This study constitutes an important first step towards establishing psychiatric traits that are of biological relevance.

Keywords: Dimensional, OCD, Compulsive, Depression, RDoC
Supported by: Wellcome Trust 101521/Z/12/Z

101. Frontostriatal Circuits in Habits and Tics

Tiago V. Maia

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Background: Frontostriatal circuits have been implicated in reinforcement learning and in several neuropsychiatric disorders, including Tourette syndrome. We conducted two fMRI studies aimed at elucidating the mechanisms underlying the involvement of these circuits in habit learning and Tourette syndrome.
Methods: In the first study, 55 healthy participants were scanned while performing a habit-learning task. The data were analyzed using a reinforcement-learning model (Q learning) and model-based fMRI (including a model-based functional connectivity analysis). In the second study, 13 patients with Tourette syndrome were scanned while having tics, and 21 healthy controls were scanned while mimicking the patients' tics.

Results: In the first study, we found that activity in the posterolateral putamen represents the strength of habits (Q values). Furthermore, consistent with the predictions of reinforcement-learning models, learning involved increases in functional connectivity between cortical sensory/motor regions and this area of the putamen, likely representing the strengthening of S-R associations. In the second study, we found that tics involve widespread hyperactivity in the motor cortico-striato-thalamo-cortical loop, including in the putamen.
Conclusions: The first study confirmed longstanding predictions from reinforcement-learning models that habit (S-R) learning involves the strengthening of corticostriatal connections between cortical sensory/motor regions and the putamen. The second study demonstrated the involvement of the motor cortico-striato-thalamo-cortical loop, which prominently involves the putamen, in Tourette syndrome. Taken together, these two studies raise the possibility that tics may be exaggerated, abnormal motor habits that are due to an excessive and inappropriate engagement of the habit-learning system.

Keywords: Reinforcement learning, Habits, Tics, Basal ganglia
Supported by: Tourette Syndrome Association

102. Computational Process Models of Emotion-cognition Interactions

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Background: Emotions influence cognition and vice-versa. These facts and their importance for psychopathology have been recognised, but the specific processes are as yet poorly understood. I will describe a series of three studies, on how Pavlovian-instrumental transfer (PIT) relates to depression and then a quantitative computational process model for how goal-directed planning is profoundly shaped by emotional processes.
Methods: 25 patients with depression and 40 controls performed a Pavlovian-Instrumental transfer task that discriminates between approach and withdrawal behaviours. Patients were followed up for 4 months. 46 and 37 subjects performed a planning task, the latter during fMRI. Process models of the Pavlovian influence on internal choices were compared with computational modelling and Bayesian model selection.
Results: Action-specificity in PIT predicted recovery. The predictive component was driven by the modulation of withdrawal. Computational models identified a Pavlovian aversive inhibition of thoughts--emotional pruning
of decision-trees--in healthy subjects that related to subclinical psychopathology and was accompanied by subgenual cingulate BOLD. The Pavlovian influence was even present within an hierarchical decomposition of the task.
Conclusions: Motivated by serotonin's relationships with inhibition, aversion and antidepressant effects, we formulated an explicit process model of how emotional information shapes thought processes or 'future-thinking' in the form of pruning. The influence is extremely robust, relates to subgenual cingulate activity and subclinical psychopathology. It is likely one central mechanism by which overly complex problems are cut down to a manageable shape by emotions, identifying a novel role for emotions in complex cognition and giving theoretical reasons for why and how emotional disturbance influence cognition.

Keywords: Emotion-cognition interaction, PIT, Depression, Computational modelling, reinforcement learning
Supported by: British Academy, Wellcome Trust and Max Planck Society

ORAL SESSION
Stress, Trauma, Fear

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Library – Mezzanine
Chair: Isabelle M. Rosso

103. Assessment of Myelin Compromise in Mild Traumatic Brain Injury with Quantitative Susceptibility Mapping

Rajendra A. Morey[1], Courtney C. Haswell[2], Wei Li[3], Shannon K. Bealll[4], Cassidy R. Fox[2], Christine E. Marx[1], Chunlei Liu[4]

[1]Psychiatry, Duke University, Durham, NC, [2]Mid-Atlantic MIRECC, Durham VA Medical Center, Durham, NC, [3]Research Imaging Institute, UT Health Science Center San Antonio, San Antonio, TX, [4]Brain Imaging and Analysis Center, Duke University, Durham, NC

Background: Radial diffusivity (RD) is frequently cited as a proxy measure of myelin damage. However, RD does not provide a direct measure of myelin and therefore such interpretations are confounded by crossing fibers and other geometric factors. Recent developments in quantitative susceptibility mapping (QSM) offer the capability of directly imaging the large macromolecules constituting myelin that are putatively damaged in mild traumatic brain injury (mTBI). Our goal was use QSM to directly assess myelin in veterans with mTBI and compare QSM with RD.
Methods: Veterans who served in Iraq and Afghanistan (n = 64) with mTBI (n = 43) and non-TBI controls (n = 21) were assessed with QSM and diffusion tensor imaging (DTI). Voxels with low QSM or RD values ($z > 2.0$) relative to the control group that clustered in 25-50 voxels (small potholes), 50-75 voxels (medium potholes), or 75-100 voxels (large potholes) were calculated for TBI subjects and using leave-one-out for non-TBI controls. The number of QSM and RD potholes were compared between groups.
Results: Veterans with mTBI had significantly more potholes than non-TBI controls [$F(1,59) = 5.0$; $p = .03$] whereas the number of RD potholes were not significantly different between groups [$F(1,59) = .837$, $p = .36$].
Conclusions: Mild TBI was associated with myelin disruption that was assessed with QSM but not detected with RD obtained from DTI. QSM shows promise for measuring myelin integrity in mTBI, whereas interpreting RD increase as a measure of myelin disruption should be undertaken with caution.

Keywords: traumatic brain injury, myelin, quantitative susceptibility mapping, radial diffusivity, TBI
Supported by: 5R01NS086885-02; 5I01RX000389-03

104. Social Cognition Rehabilitation with Veterans with Comorbid Traumatic Brain Injury and Posttraumatic Stress Disorder: Preliminary Data and Clinical Trial Design

Laura A. Thomas[1], Kelly McCarron[2], Megan Dasgupta[2], Christopher Hansen[1], Matthew Reinhard[1]

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Background: Veterans returning from the Global War on Terror present with complex comorbid injuries that challenge existing treatment paradigms, including high concordance of Traumatic Brain Injury (TBI) with Posttraumatic Stress Disorder (PTSD). While veterans with TBI and PTSD present with significant social cognition deficits, mood disruptions, and decreased social functioning, there are currently no social cognition rehabilitations targeted at this population.
Methods: Five veterans were recruited through referral from Polytrauma Network Site clinicians at the Washington, D.C. Veterans Affairs Medical Center (DCVAMC), based on TBI with ongoing neurocognitive symptoms, psychological trauma with ongoing mental health symptoms, and social functioning deficits in daily life. This 12-month pilot group utilized the "Social Cognition Rehabilitation for Veterans with TBI and PTSD: A Treatment Workbook" by clinicians at the DCVAMC.
Results: Significant improvements post vs. pre-treatment were found on the Quality of Life after Brain Injury, Mayo-Portland Adaptability Inventory, Interpersonal Reactivity Index, and the Weschler Social Perception Task. There was a trend for improvement on the Social Functioning Scale. Scores on the Beck Depression Inventory were significantly improved and trended to improve on the Beck Anxiety Inventory.
Conclusions: The pilot Social Cognition Rehabilitation demonstrated improvement and life successes for the veterans who participated. A clinical trial is being developed using this intervention to rehabilitate social deficits in TBI and PTSD by addressing social cognition. If validated, this Rehabilitation could be implemented within existing VA health care systems, and eventually to civilians, lessening the high economic cost and heavy social burden of TBI and PTSD.

Keywords: Traumatic Brain Injury, Posttraumatic Stress Disorder, Social Cognition, Rehabilitation, clinical trial

105. Genome-Wide Differential Gene Expression in Comorbid PTSD and Depression Post Trauma Exposure

Aliza P. Wingo[1,2], Lynn Almli[1], Sumeet Sharma[1], Alicia Smith[1], Jennifer Leveille[1], Kimberly Kerley[1], Bekh Bradley[1], Elisabeth Binder[1], Greg Gibson[3], Kerry Ressler[1]

[1]Psychiatry, Emory University, Atlanta, GA, [2]Mental Health, Atlanta VAMC, Atlanta, GA, [3]School of Biology, Georgia Institute of Technology, Atlanta, GA

Background: PTSD and depression are highly comorbid and prevalent among individuals exposed to traumatic experiences. Since diagnostic criteria for psychiatric disorders are based on descriptive studies, distinctions among disorders can be arbitrary, and symptoms overlap among disorders. It is therefore possible that the common psychological sequelae of trauma exposure – comorbid PTSD and depression- constitute a cohesive biological entity. We aimed to elucidate biological mechanisms underlying comorbid PTSD/depression post trauma exposure.
Methods: PTSD and depression were assessed with the PTSD Symptoms Scale and Beck Depression Inventory in 184 inner-city participants. We compared genome-wide blood gene expression profiles between 112 cases of PTSD/depression and 72 controls, covarying for sex, age, substance use, and population stratification.
Results: At FDR of 0.05 two genes were significantly differentially expressed between cases and controls, with Dicer1 having decreased expression (p=1.17E-05) and MRPS23 increased expression (p=1.08E-05) in cases. Follow-up studies found that a Dicer1 snp, rs10144436, located in 3'UTR, significantly correlated with Dicer1 expression (p=0.0059, Bonferroni p=0.035). Moreover, this eQTL snp was significantly associated with comorbid PTSD/depression (p=0.034).
Conclusions: Complementary to this, our group found that Dicer1 expression was decreased in the amygdala in fear-conditioned mice versus controls, and Dicer1 mRNA levels in blood significantly correlated with that in the amygdala. Additionally, Dias et al observed that stress resilience was mediated through Dicer1/microRNA regulation in mice. Taken together, these findings suggest DICER1 may play an important role in the biological mechanism of comorbid PTSD/depression, likely through gene expression regulation via micro and small interfering RNA.

Keywords: genome-wide gene expression, PTSD depression, post trauma
Supported by: IK2CX000601;MH071537;MH096764; NARSAD

106. Specific and General Deficits in Cognitive Functions among MDD, PTSD and Healthy Controls: Behavioral and Resting-state Evidence

Julia Huemer[1,2,3], Anett Gyurak[1,2], Brian Patenaude[1,2], Jane Zaiko[1,2], Kathy Peng[1,2], Meredith Harvey[1,2], Greg Fonzo[1,2], Madeleine Goodkind[1,2], Amit Etkin[1,2]

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Background: Previous work documented broad-based deficiencies in cognitive functions in Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD) behaviorally and neurally. Little work assessed these patient groups using the same standardized set of cognitive function measures and compared the functioning of brain networks across and between these groups.
Methods: We present results from a study where unmedicated MDD (N=27), PTSD (N=30), MDD/PTSD comorbid (N=27) patients and healthy controls (HC) (N=36) were compared on standardized behavioral assessments of cognitive functions. Brain network integrity was assessed using Functional Connectivity (FC) and graph analyses in a resting-state task. Reported results were significant in separate 2x2 ANOVAs.
Results: Results revealed that in terms of cognitive functions, PTSD patients had lower sustained attention, slower processing speed, and lower memory recall. All patients showed decreased Default Mode Network (DMN) FC, PTSD patients additionally showed

lower visuospatial (VS) network connectivity. Poor cognition related to more abnormal VS-DMN connectivity. Graph analyses revealed a significant patient-specific difference in terms of weighted mean clustering coefficient, overall and for the VS network, and weighted mean participation coefficient overall, and for the executive control and salience network. Assortativity differed significantly in MDD patients, and mean weighted participation coefficient in PTSD patients.
Conclusions: These results show that deficits in cognitive functions are pervasive in MDD and PTSD. The functioning of the networks that support these operations are also perturbed across these disorders. Findings suggest some specific, as well as some general deficits between and across patient groups.

Keywords: Brain networks, Functional connectivity, Graph analyses, Cognition, Resting-state
Supported by: R21 MH097984; R01 MH091860

107. Gender-Specific Influence of Type and Timing of Childhood Maltreatment on Caudate, Putamen and Nucleus Accumbens Volume

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Background: Childhood maltreatment is associated with increased risk for substance abuse, affective and psychotic disorders, which may be attributable to influence of early stress on striatal development. We assessed the extent to which striatal volumes could be 'predicted' from retrospective information on type and timing of maltreatment.
Methods: FreeSurfer was used to determine volumes from 3T MRIs collected on 301 subjects (18-25 years) recruited to provide equal cell sizes for exposure to 0-4 plus types of maltreatment. The Maltreatment and Abuse Chronology of Exposure Scale was used to assess severity of exposure to ten types of maltreatment across each year of childhood. Importance of type and timing was evaluated using random forest regression with conditional trees and cross-validated.
Results: Clear evidence emerged for sensitive periods when exposure to a particular type of maltreatment at 1 or 2 adjacent ages was a more significant predictor of volume that duration, severity or multiplicity of maltreatment types across childhood. Robust and discrete sensitive exposure periods were apparent in male caudate (parental verbal abuse at age 6 bilaterally), putamen (peer emotional abuse age 14 females, emotional neglect age 2 males), and accumbens (physical maltreatment and non-verbal emotional abuse ages 4-7 males bilaterally, emotional neglect age 2 females right side).
Conclusions: These findings are consistent with the hypothesis that trajectories of striatal development might be affected by exposure to specific types of maltreatment during discrete sensitive exposure periods, and help explain why maltreatment is a risk factor for a host of different psychiatric disorders.

Keywords: Abuse and Neglect, Trauma, Striatum, Maltreatment, Early life stress
Supported by: R01 MH091391; R01 DA-017846

108. Low Behavioral Pattern Separation Is Linked to Reduced Dentate Gyrus Activation During Fear Generalization

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Background: Fear overgeneralization has been implicated as a central factor in the development of anxiety disorders. Pattern separation, a hippocampal-dependent mechanism by which new and familiar sensory inputs can be separated, could be an underlying mechanism of fear generalization. The current study examines whether behavioral pattern separation is associated with dentate gyrus (DG) activation during an fMRI conditioned fear generalization task.
Methods: Sixty healthy volunteers aged 16-25 conducted a computerized task to tax behavioral pattern separation and an fMRI fear conditioning and generalization task. During the latter task, seven circles/rectangles, parametrically increasing in size, were shown. The smallest and largest shapes served as safety (CS-) and danger stimuli (CS+), the intermediate sized shapes as generalization stimuli (GS1-5).
Results: Generalization gradients in behavioral fear ratings and brain activation in bilateral DG and insula were found. Activation in DG gradually increased for stimuli that were less similar to the CS+. As hypothesized, this increase in the DG was statistically significant different between high and low scorers on the behavioral pattern separation task: participants with a low score showed reduced left DG activation for all stimuli compared to the CS+ ($p<.01$). However, no differences in self-reported fear ratings between high and low behavioral pattern separation scorers were found.
Conclusions: This is the first study to demonstrate that pattern separation mechanisms in the DG are implicated in the process of human conditioned fear generalization. Future studies are needed to elucidate the transition from dysfunctional pattern separation towards conscious fear experience in the brain.

Keywords: fear generalization, pattern separation, fMRI, dentate gyrus
Supported by: Weijerhorst Foundation

109. Exposure to Glucocorticoids During Hippocampal Neurogenesis and Childhood Maltreatment: Mechanisms of System Wide Epigenetic Effects

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Background: Excessive glucocorticoids (GC) release after early life stress exposure is thought to result in a long-lasting disruption of the stress hormone system and ultimately to an increase risk

for psychiatric disorders later in life. Stress and GCs are known to regulate hippocampal neurogenesis and to induce long-lasting changes in DNA methylation in specific loci such as the glucocorticoid receptor (NR3C1) and FK506 binding protein 5 (FKBP5) in hippocampal but also in peripheral blood cells DNAs. Here we aim to expend these results to multiple loci using whole genomic comprehensive analysis of the epigenetic effects of GC activation during hippocampal neurogenesis and child abuse in adult blood.
Methods: We used Illumina arrays to analyse gene expression and CpG methylation levels of immortalised human hippocampal progenitor cells (HPC) treated with dexamethasone (Dex) or vehicle at different stages during neurogenesis and adults exposed or not to severe child abuse (n=415).
Results: Our preliminary results revealed an effect of Dex treatment on the DNA methylation levels of more than 5000 CpG sites (Pvalue < 0.05 and FDR < 0.05) during hippocampal differentiation where a significant portion of these alterations where maintained after differentiation including CpGs in the FKBP5 locus. Part of these differentially methylated CpG sites in the HPCs following Dex treatment were also differentially methylated in blood cells of adult exposed to child abuse.
Conclusions: These preliminary analyses provide evidence of clustered and genome-wide epigenetic effects of GC activation during hippocampal neurogenesis where the timing of the exposure seems to be critical to induce long-lasting changes.

Keywords: epigenetics, glucocorticoid, DNA methylation, hippocampal progentitor cells, child maltreatment
Supported by: ERC grant GxE molmech

110. Brain Correlates of the Interaction Between 5-HTTLPR and Psychosocial Stress Mediating Attention-deficit/hyperactivity Disorder Severity

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Background: Serotonin transporter 5-HTTLPR genotype has been found to moderate the effect of stress on severity of attention-deficit/hyperactivity disorder (ADHD), with stronger effects of stress in carriers of the short allele than in individuals homozygous for the long allele. The underlying neurobiological mechanism of this gene-environment interaction in ADHD is unknown. This study aimed to determine whether 5-HTTLPR moderates the effect of stress on brain grey matter volume and, if so, which brain regions mediate the effect of this gene-environment interaction on ADHD severity.
Methods: Structural magnetic resonance imaging, 5-HTTLPR genotype, and stress exposure questionnaire data were available for 701 adolescents and young adults participating in the multicenter ADHD cohort study NeuroIMAGE (from 385 families; 291 with ADHD, 78 with subthreshold ADHD, 332 healthy controls; 55.8% males; average age 17.0 years). ADHD symptom count was determined through multi-informant questionnaires. For the analysis, we combined a whole-brain voxel-based morphometry approach with mediation analysis.
Results: Stress exposure was associated with significantly less grey matter volume in the precentral gyrus, middle and superior frontal gyrus, frontal pole, and cingulate gyrus for S-allele carriers than for participants homozygous for the L-allele. The association of this gene-environment interaction with ADHD symptom count was mediated by grey matter volume in the frontal pole and anterior cingulate gyrus.
Conclusions: 5-HTTLPR genotype moderates the effect of stress on brain regions involved in social cognitive processing and cognitive control. Specifically regions important for cognitive control link this gene-environment interaction to ADHD severity.

Keywords: ADHD, gene-environment interaction, Neuroimaging, Serotonin transporter gene, Stress exposure
Supported by: NIH Grant R01MH62873

LATE BREAKING
Late Breaking Oral Session

Thursday, May 14, 2015, 3:00 PM – 5:00 PM
Tudor 8 – Main Mezzanine
Chair: David C. Glahn

The Late Breaking oral abstracts (No. 111 through 118) were accepted after this supplement was published. See the On-Line Program Planner or Mobile App for the complete abstract.

POSTER SESSION
Thursday

Thursday, May 14, 2015, 5:00 PM – 7:00 PM
Concert Hall – Convention Floor

119. Modulating Extinction of Conditioned Fear by Transcranial Direct Current Stimulation

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Background: Exposure-based therapy parallels extinction learning of conditioned fear in that both rely on the repeated exposure to feared stimuli without the occurrence of the feared consequences. Data from animal and human studies point to the ventromedial prefrontal cortex (vmPFC) as a potential site for the consolidation of extinction learning and subsequent retention of extinction memory. In the present study we explored whether non-invasive electrical stimulation, i.e. transcranial Direct Current Stimulation (tDCS), during extinction can improve extinction learning and subsequent extinction recall in human participants.
Methods: 44 healthy volunteers completed a 2-day Pavlovian fear conditioning, extinction, and recall paradigm while skin conductance activity was continuously measured. 26 participants received 2 mA anodal tDCS over FA3 targeting the vmPFC immediately at the onset of extinction learning. The remaining 18 participants received similar tDCS starting halfway through extinction learning (sham stimulation was applied for the balance of extinction trials). Normalized skin conductance changes were analyzed using linear

mixed models to specifically evaluate effects of tDCS on late extinction and early recall.
Results: During late extinction, there was a significant interaction between timing of tDCS and skin conductance changes over repeated trials ($F(5,210)=2.44$, $p=0.035$). No significant effects of tDCS timing were observed for early extinction learning, early extinction recall or late
extinction recall.
Conclusions: These data show a continued reduction in skin conductance reactivity during late extinction after tDCS consistent with a temporal effect of electrical stimulation observed in rats. Hence, tDCS appears to accelerate extinction learning potentially due to tDCS aftereffects driven by synaptic modification.

Keywords: Fear extinction, Neuromodulation, Anxiety, Medial prefrontal cortex, Direct Current Stimulation
Supported by: NARSAD Young Investigator Award

120. Impaired Acquisition of Classically Conditioned Fear-potentiated Startle Reflexes in Humans with Focal Bilateral Basolateral Amygdala Damage

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Background: Based on studies in rodents the basolateral amygdala (BLA) is considered a key site for experience-dependent neural plasticity underlying the acquisition of conditioned fear responses. In humans, very few studies exist of subjects with selective amygdala lesions and those studies have only implicated the amygdala more broadly leaving the role of amygdala sub-regions underexplored.
Methods: We tested a rare sample of subjects (N = 4) with unprecedented focal bilateral BLA lesions due to a genetic condition called Urbach-Wiethe disease in a classical delay fear conditioning experiment. In these subjects and a group of matched control subjects (N = 10) fear-potentiation of the eye-blink startle reflex was taken as index of fear conditioning.
Results: BLA-damaged subjects showed impaired acquisition of conditioned fear relative to controls (Mann-Whitney test, $p = .03$). After the experiment the BLA-damaged subjects showed normal declarative memory of the conditioned association (Fisher's exact test, $p = .58$).
Conclusions: Our findings provide new evidence that the human BLA is essential to drive classically conditioned defensive reflexes, but is dispensable for declarative fear memory formation.

Keywords: Amygdala, Fear, Startle, Conditoining, Lesion

121. White Matter Connectivity and Attentional Control in Traumatized Adults with and without Posttraumatic Stress Disorder

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Background: Abnormalities in attentional control characterize posttraumatic stress disorder (PTSD), and lead to impairments in both cognitive and emotional processes. It is possible that decrements in the integrity of particular white matter pathways, specifically, those that serve to connect prefrontal and limbic regions, support these problems; however, this has not been examined in the current literature. This was the objective of the present study.
Methods: Behavioral and Diffusion Tensor Imaging (DTI) data was collected from 28 women age 22-58 (M=36) as part of an ongoing study of risk for PTSD. Probabilistic tractography was used to examine connectivity of uncinate fasciculus (UF) and cingulum tracts. We employed the Affective Number Stroop task, which requires participants to ignore positive, negative, and neutral distracting images as they engage in an attentional task that has both low and high cognitive demand conditions. The PTSD symptom scale (PSS) was used to assess current PTSD symptoms, and the Beck Depression Inventory was used to assess current depressive symptoms.
Results: Participants with PTSD performed more poorly on the task, irrespective of distractor type (all ps $<.05$). After controlling for depressive symptoms, connectivity in the UF was inversely associated with number of errors on positive distractor trials that had higher cognitive demands ($r=-.56$, $p=.04$).
Conclusions: Decrements in the architecture of a primary connection between limbic and prefrontal brain regions may lead to poorer attentional control in the face of positive emotion. We will discuss how this may represent a biological marker of increased vulnerability for PTSD.

Keywords: Diffusion tensor imaging, Posttraumatic stress disorder, Attention, Cognition, Tractography
Supported by: K23MH101380

122. Design and Validation of a Human MRI Battery for Longitudinal Stress Resilience Studies: Testing Positive Appraisal Style Theory of Resilience

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Background: There is currently no accepted, unifying theory of resilience and a dearth of methodologically rigorous longitudinal studies. We have recently proposed a dedicated methodological framework and a new mechanistic theory that emphasizes

conscious and non-conscious processes of positive stressor appraisal and reappraisal and their neurobiology. The framework explicitly supports translational investigation.
Methods: In n=40 healthy human subjects, we are developing a 2-day structural and functional MRI battery, supplemented by behavioral testing, that can be repeatedly applied to subjects during longitudinal monitoring of real-life stressor exposure and changes in mental health. The battery includes resting-state and task-based fMRI, with a focus on implicit and explicit (re)appraisal processes (a.o., threat discrimination, fear extinction, volitional reappraisal (distancing and situation-focused reappraisal)) and auxiliatory interference inhibition processes. Factor analysis will be used to identify latent constructs which we predict to map onto different dimensions of positive (re)appraisal and to mediate the influence on mental health outcomes of known resilience factors like social support, personality, or genotype.
Results: Pilot testing (n=13) demonstrates feasibility and suggests robust behavioral effects in the employed tasks [e.g., extinction learning (decay of CS+ SCRs: p=0.037, n=8 subjects with valid SCR data) and recall (ext. vs. non-ext. CS+ SCRs: p=0.069, n=8), affective interference in stop-signal task (p=0.002, n=13)].
Conclusions: Assessing positive (re)appraisal processes at a behavioral and neural level is possible. The current results provide a basis for validating the piloted MRI battery in an extended sample (n=40), including factor analysis, to thus derive precise experimental predictions for longitudinal testing.

Keywords: resilience, stress, appraisal, extinction, fMRI
Supported by: Stiftung RLP für Innovation

123. Childhood Emotional Neglect and Trait Resilience are Related to Ventromedial Prefrontal Cortex Volume in PTSD

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Background: Child maltreatment has been linked to deficits in ventromedial prefrontal cortex (vmPFC) brain volume. This region is also implicated in coping and resilience, as stress resistance depends on vmPFC inhibitory control over brainstem and limbic structures. However, little research has concurrently explored the effects of early life stress and resilience factors in posttraumatic stress disorder (PTSD) patients. We hypothesized that current PTSD symptomology and early life stress would be related to decreased vmPFC volume, while resilience would be related to increased vmPFC volume.
Methods: We conducted a retrospective study with 20 subjects with a history of childhood trauma. PTSD symptoms were assessed with the Clinician Administered PTSD Scale (CAPS). Subjects also completed the Childhood Trauma Questionnaire (CTQ), which has subscales emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse, and the Connor-Davidson Resilience Scale. All subjects underwent 3T magnetic resonance imaging and vmPFC volumes were determined using FreeSurfer software.
Results: The emotional neglect subscale of the CTQ, but not other subscales, was negatively correlated with vmPFC volume (r(19)=-.67, p=.001). Childhood emotional neglect (Beta=-.68, p<.001) and age of first trauma (Beta=-.43, p=.001) predicted vmPFC volume (R2=.38, F(2,25)=7.78, p=.002). vmPFC volume was also positively related to trait resilience (r(19)=.45, p=.04) and negatively related to CAPS hyperarousal symptoms (r(19)=-.47, p=.04).
Conclusions: This study identifies childhood emotional neglect as having the largest effect on vmPFC volume. Emotional neglect presumably reduces opportunities for stress resistance learning from caregivers, which is reflected by reduced vmPFC volume, heightened hyperarousal symptoms, and impoverished trait resilience.

Keywords: PTSD, Childhood maltreatment, Resilience, ventromedial prefrontal cortex
Supported by: R01MH096987-02

124. Autonomic Modulation of Neural Responses During Fear Extinction Recall

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Background: Autonomic responses reflect emotional reactions to fearful events. Skin conductance response (SCR) is one widely used autonomic measure. Functional magnetic resonance imaging (fMRI) research in adults delineates brain regions that modulate SCR, including the amygdala. The present study extends these prior findings using a task that is appropriate for children.
Methods: 16 adults (M=24.01±2.36 years) and 4 children (M=13.29±0.97 years) underwent fear conditioning and extinction. During acquisition, participants viewed two different colored bells, the CS, one of which, the CS+, was paired with the UCS, an alarm sound. During extinction, the CS+ and CS- were presented without the UCS. Ten to 30 days later, participants returned for the extinction recall task in the fMRI scanner, when they viewed the CS+ and CS- and four morphed images consisting of CS+/CS- blends, while making a threat appraisal or memory rating. We examined neural activity associated with fluctuations in SCR amplitude in response to each morph.
Results: SCRs at acquisition were larger to the CS+ than CS- (M=.23 vs .15, p< .05). During extinction, no SCR differences were observed (M=.19 vs .18). At extinction recall, participants correctly recalled the CS+ versus the four morphs (p <.05) but not versus the CS- (p=.29). Covariance between SCR and activity in bilateral amygdala, anterior insula and anterior cingulate was observed for the attention x morph interaction.
Conclusions: Our results indicate that a set of brain areas is involved in somatic arousal during retrieval of extinguished fear. Implications for understanding of anxiety disorders will be discussed.

Keywords: fear conditioning, functional magnetic resonance imaging, skin conductance, extinction recall
Supported by: NIMH Intramural Funding

125. Dynamic Network Analysis Uncovers the Neural Correlates of Alexithymia

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Background: The ability to understand and describe emotions plays a key role in the ability to withstand stressful life events. Alexithymia stands for a deficiency in understanding and describing emotional feelings. Accumulating evidence has linked alexithymia with core brain-areas related to emotion generation and regulation such as the amygdala, the Anterior-Cingulate-Cortex (ACC) and the medial-Prefrontal-Cortex (mPFC). However, both positive and negative relationships between alexithymia and activity in these areas was reported. The current study examined whether previous findings are not contradictory but rather represent processes of distinct temporal aspects. Considering the dynamic nature of the emotional experience and its neural mechanisms, we assumed that by using a film as a dynamic emotional stimulus and a multimodal data analysis method, the neural correlates of alexithymia could be uncovered. We hypothesized that in different stages of the emotional experience alexithymia will predict distinct synchronization patterns of neural-networks involved in either emotion generation or regulation.
Methods: During fMRI scanning, 51 participants watched an emotionally stimulating video and rated emotional-intensity. Network synchronization was analyzed using the Network-Cohesion-Index (NCI).
Results: During the most emotionally stimulating moments of the film high alexithymia predicted low synchronization ($r=0.5, p<0.03$) between executive networks related to emotion regulation. Throughout the film alexithymic subjects exhibited high volatility in the synchronization ($r=0.4, p<0.04$) of the limbic network.
Conclusions: We suggest that alexithymia reflects abnormal synchrony patterns of neural networks involved in emotion generation and regulation. At different stages of the emotional experience these abnormalities result in deficits at either recognizing or expressing emotions.

Keywords: Alexithymia, Network, Cohesion, Connectivity
Supported by: DOD

126. The Relationship Between ELS and PTSD Among ED Trauma Victims

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Background: Trauma exposure early in life (early life stress or ELS) is associated with an increased risk for post-traumatic stress disorder (PTSD). Despite this increasingly well documented relationship, the specific types of ELS associated with PTSD is less well understood. We examined the relationship between ELS subtypes and PTSD.
Methods: 100 participants, aged 18-65 years, were recruited from the Emergency Department (ED) following exposure Criterion A trauma. 47 participants were assessed for ELS using the Childhood Trauma Questionnaire (CTQ) and assessed for PTSD 3 months later using the PTSD Symptom Scale. The CTQ was used to group participants according to a positive history of emotional, physical, sexual abuse and/or neglect. Chi-square tests were calculated.
Results: Childhood emotional abuse (n=6) was significantly associated with PTSD development (31.8 vs 3.6; $p<0.05$). Childhood sexual abuse (n=9) was also significantly associated with PTSD development at 3 months (47.4 vs 7.2; $p<0.05$). Adults with childhood emotional abuse had higher odds of developing PTSD even after controlling for demographic factors (OR 27.9; CI: 1.4, 568.5). Adults with childhood history of sexual abuse also had significantly higher odds of developing PTSD after controlling for demographic factors (OR: 9.6; CI: 1.3, 69.2). Other forms of childhood trauma such as neglect and physical abuse were not purely associated with PTSD.
Conclusions: Preliminary findings from the present study indicate that specific subtypes of ELS may increase vulnerability to PTSD. Although further study is needed, the present results indicate that a history of ELS may indicate the need for immediate intervention to prevent PTSD.

Keywords: PTSD, ELS, Anxiety, Trauma, Abuse
Supported by: R01 MH094757

127. Opposing Effects of Negative Emotion on Item and Associative Memory are Predicted by Changes in Amygdala and Hippocampal Activity

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Background: Understanding the neural mechanisms that underpin emotional memory formation can provide important insight into memory disturbances in clinical disorders, such as PTSD. We contrasted two accounts of emotional memory, one proposing memory enhancements that generalise across the whole event and the other predicting item memory enhancement accompanied by associative memory impairment.
Methods: Using fMRI, we examined encoding and retrieval of paired associates made up of all four combinations of neutral and negative images. At test, participants were cued with an image and, if they recognised it from encoding, had to retrieve the associated (target) image.
Results: Performance across item recognition and associative retrieval in all four types of pairs reflected two factors: increased item memory for negative images and reduced associative memory for pairs that included a negative image. At encoding, subsequent item recognition was correlated with amygdala activity, while associative memory was correlated with hippocampal activity. Hippocampal activity was reduced by the presence of negative images, during encoding and during correct associative retrieval. By contrast, amygdala activity increased for correctly retrieved negative images, even when cued by a neutral image.
Conclusions: Our findings support a dual representation account, in which negative emotion up-regulates the amygdala to strengthen sensory/perceptual representations of negative items but down

regulates the hippocampus to weaken associative/contextual representations. These results highlight important implications for the development of clinical disorders in which diminished associations between emotional stimuli and their context might be considered an important vulnerability, such as PTSD.

Keywords: Amygdala, Hippocampus, Memory, PTSD
Supported by: UK Medical Research Council; Wellcome Trust UK

128. Effects of 7.5% CO2 Inhalation on Stress, Anxiety, Autonomic Arousal and Executive Function

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Background: Stress and anxiety have various effects on cognitive and emotional processes. For example, acute stress enhances memory consolidation, but reduces retrieval. Anxiety has been associated with attentional hypervigilance, particularly to negative information, and poor attention control. However, the influence of acute stress and anxiety on executive function requires clarification. One experimental model to elicit stress and anxiety in a reliable and objective way is the inhalation of air enriched with 7.5% CO2. We investigated how acute stress and anxiety induced by CO2 inhalation affects cognitive flexibility and response inhibition.
Methods: In a single-blind (quasi-)placebo-controlled within-subject crossover study, 44 healthy participants (mean age 29, 22 female) performed parallel versions of the CANTAB attentional set-shifting task (ID/ED) and the affective Go/No-go task (AGN, positive/negative words) during inhalation of air enriched with CO2 (7.5% CO2, 21% O2, 71.5% N2), and, in a counterbalanced order, during inhalation of normal air. Additionally, blood pressure, heart rate and subjective measures of anxiety and affective state were taken. Data were analysed using a repeated-measures factorial ANOVA.
Results: CO2 inhalation increased subjective anxiety and negative affect and decreased positive affect. Blood pressure and heart rate increased during CO2 inhalation. In the ID/ED task, CO2 increased the number of extra-dimensional, but not intra-dimensional shift errors. In the AGN, CO2 inhalation increased the number of omission errors, independent of valence, and slowed the correct response latency to positive words.
Conclusions: Acute stress and anxiety induced by CO2 inhalation impaired executive functions by reducing cognitive flexibility and decreasing sustained attention.

Keywords: anxiety, stress, executive function, cognition, flexibility
Supported by: RG59107

129. Oxytocin Modulates Pavlovian Fear Conditioning and Extinction in Humans

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Background: The neuropeptide oxytocin is thought to promote human sensitivity to social cues, thus improving neural processing of these stimuli in situations associated with heightened endogenous oxytocin release. We have recently shown that intranasal oxytocin (IN-OT) promotes Pavlovian fear extinction via suppression of amygdala responses to the conditioned stimulus (CS+) and concomitant upregulation of top-down control from prefrontral cortex. Less clear is the influence of IN-OT on Pavlovian fear conditioning. While there is evidence for anxiolytic-like effects of IN-OT as a result of amygdala inhibition, some studies have shown that the peptide can strengthen defensive abilities in social contexts, an effect mediated by upregulation of extra-amygdalar brain regions.
Methods: In the present randomized controlled study involving 97 healthy male subjects, we employed functional MRI (fMRI) and simultaneous skin conductance response (SCR) measures to examine the neuromodulatory influence of IN-OT (24 IU) on Pavlovian fear conditioning.
Results: We found that IN-OT strengthened Pavlovian fear conditioning on both the behavioral and neural level. Relative to placebo treatment, subjects exhibited faster task-related responses and a larger increase in SCRs to the CS+, which was paralleled by heightened activity in cingulate cortex subregions in the absence of changes in amygdala function.
Conclusions: Collectively, our experiments indicate that IN-OT facilitates both Pavlovian fear conditioning and extinction in healthy male subjects. This speaks against amygdalocentric views of oxytocin as having pure anxiolytic-like effects. Instead, it suggests that the peptide enables rapid and flexible adaptation to fear signals in social contexts, which may have conferred evolutionary advantages.

Keywords: Fear conditioning, fMRI, oxytocin, psychophysiology
Supported by: R.H. was supported by a Starting Independent Researcher Grant ('NEMO – Neuromodulation of Emotion') jointly provided by the Ministry of Innovation, Science, Research & Technology of the German State of North Rhine-Westphalia (MIWFT).

130. Anxious Individuals Have Difficulty Learning the Causal Statistics of Aversive Environments

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Background: Statistical regularities in the causal structure of the environment enable us to predict the probable outcomes of our actions. Environments differ in the extent to which action-outcome contingencies are stable or volatile. It is thought that adaptation of learning in stable vs. volatile environments is mediated by central

norepinepherine, which may be estimated using pupillometry. Difficulty in being able to adapt learning optimally in response to volatile environments might contribute to the decision-making difficulties seen in anxiety.
Methods: We tested this hypothesis using an aversive learning task which manipulated environmental volatility. 31 (22 female, mean age 23.7 years) non-clinical participants were recruited on the basis of their trait anxiety (measured using the trait-STAI) and completed the task while pupil diameter measurements were recorded. Data were analysed by fitting a computational learning model to participant's behavioural and eyetracking data and then testing whether the parameters of the models correlated with trait anxiety.
Results: Low anxious participants matched updating of their outcome predictions to the volatility of the current environment, as predicted by a Bayesian model. High anxious individuals showed less ability to adjust updating of outcome expectancies between stable and volatile environments [p=0.02]. This was linked to reduced sensitivity of the pupil dilatory response to volatility in the high anxious participants [p=0.005].
Conclusions: These results indicate that the learning difficulties of anxious individuals may arise from altered noradrenergic responsivity to changes in environmental volatility.

Keywords: Anxiety, Learning, Computational Neuroscience, Norepinepherine
Supported by: GA260932 ; R01MH091848

131. Body-focused Repetitive Behaviors (Hair-pulling, Skin-picking, Onychophagia) and Dissociation: An Under-recognized Association

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Background: Obsessive-Compulsive and Related Disorders (DSM-5) include body-focused repetitive behaviors (BFRB) that primarily involve the integumentary system. Automatic skin-picking or hair-pulling without preceding tension and without full awareness (DSM5) have been described as features of the BFRB(DSM-5)with no specific mention of dissociation. Few studies have examined dissociation in the BFRB, especially trichotillomania. The skin is a large sensory organ with afferent sensory nerves conveying multiple sensory modalities to the CNS and efferent autonomic mainly sympathetic nerves, and can play a role in emotional regulation. We examined the relationship of BFRB involving the skin, hair and nails, to dissociation.
Methods: 352 consecutive consenting volunteers (42 psychiatric outpatients, 310 community-based non-clinical subjects; 75.9%female; mean±SD age: 39.09±14.22) completed a battery of instruments including the Dissociative Experiences Scale(DES) and the 'BFRB Scale' which addressed picking of the integument (skin-picking, hair-pulling, nail-biting) under stress and difficulty stopping once the behavior is initiated. These symptom dimensions all fall in the obsessive-compulsive spectrum and support the DSM-5 definition of BFRB.
Results: Multiple regression analysis using 'BFRB Scale' score as dependent variable and Community_versus_ Psychiatric status, sex, age, and DES scores as independent variables revealed that Psychiatric status (β=0.15, t=2.97, p=0.003), female gender (β=0.11, t=2.14, p=0.033), younger age (β=-0.15, t=-2.89,p=0.004) and DES scores (β=0.30, t=5.82, p<0.001) were all predictors of BFRB.
Conclusions: Dissociation is an important but under-recognized feature of the BFRB. This has important treatment implications, as patients with high levels of dissociation are not likely to respond to the standard treatments for obsessive-compulsive disorder.

Keywords: Dissociation, Trichotillomania, Excoriation Disorder, Skin, Emotional Regulation

132. Overexpression of Corticotropin-releasing Hormone (CRH) in the Dorsal Amygdala Alters Anxious Temperament and Brain Metabolic Activity

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Background: Children with an extremely anxious temperament (AT) are at risk to later develop depression and anxiety disorders. We have established and extensively validated a non-human primate model of this early-life risk, and we identified the central nucleus of the amygdala (Ce) as a key component of the neural circuit that mediates AT. Corticotropin-releasing hormone (CRH) has a known role in stress and is expressed in the Ce. To understand the consequences of increased Ce-CRH in primate anxiety, we utilized viral vector technology to overexpress Ce-region CRH in young rhesus monkeys.
Methods: We studied 10 young monkeys, 5 of which received bilateral Ce-region injections (24µl/side) of an adeno-associated virus (AAV) with a CRH construct (AAV2-CRH) using magnetic resonance imaging-guided convection-enhanced delivery. The other 5 animals served as non-operated controls. Postmortem analysis in a pilot animal verified robust viral vector-induced CRH expression. Two months following virus infusion we assessed injection-induced changes in AT, and regional brain metabolism with [^{18}F]-fluorodeoxyglucose-positron emission tomography.
Results: Animals with CRH overexpression demonstrated significant increases in AT (p<0.05, one-tailed). Moreover, there was a significant injection-induced increase in Ce metabolism in the Ce-region CRH group, when compared to control animals (p<0.01, uncorrected). Furthermore, whole-brain analyses revealed increased metabolism within other AT-related regions, including: orbitofrontal cortex, hippocampus, and brainstem (p<0.01, uncorrected).
Conclusions: Taken together these results indicate that chronically increased CRH expression influences AT and metabolism within components of the AT neural circuitry. This study underscores the potential for gene delivery in primate models to elucidate the mechanisms of regional gene-expression on distributed brain

function, as well as to explore novel treatment strategies for refractory psychiatric illness.

Keywords: anxiety, stress, monkey, depression, behavioral inhibition
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133. Behavioral, Neural and Endocrine Changes Associated with Nursery/Peer Rearing in Rhesus Monkeys

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Background: Evidence suggests that early neglect is associated with maladaptive behaviors and may be an antecedent to stress-related psychopathology. We examined the extent to which nursery/peer-rearing (PR) increased anxiety-related behaviors in young monkeys that were rejected by their mothers after birth.
Methods: 50 rhesus monkeys (25 PR animals: mean age: 1.85 yrs; 7 females; and 25 matched maternally-reared controls) were tested in the no eye-contact (NEC) condition of the human intruder paradigm, a classic test of anxiety in nonhuman primates. Behavior, plasma cortisol and oxytocin levels, and brain metabolism (FDG_PET) were assessed in response to NEC, along with deformation-based morphometry, and cerebrospinal fluid (CSF) levels of corticotropin-releasing hormone (CRH) and oxytocin. The response to a live snake was also examined.
Results: We first examined the extent to which PR was associated with increased anxiety, and results demonstrated that PR animals were less anxious than controls. During NEC, and when the animals were alone, there was a small but significant decrease in the duration of freezing behavior. No differences in plasma cortisol, plasma oxytocin or CSF CRH were observed. Furthermore, there were no differences in the innate response to a snake. Supporting a reduction in anxiety, PR animals demonstrated reduced insular cortex metabolism, which was correlated with freezing behavior across the sample. Interestingly, other self-directed behaviors, such as thumb sucking, were increased. At a physiological level, PR was associated with reduced CSF oxytocin levels and structural brain changes.
Conclusions: Taken together, these results indicate significant effects of PR on behavior, brain structure, and CSF levels of oxytocin. However, PR animals appeared less anxious than controls in response to a human intruder.

Keywords: anxiety, early adversity, brain imaging, oxytocin, primate
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134. Effects of Early Life Trauma on Affective Executive Control and White Matter Integrity in Veterans with and without PTSD

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Background: Prior studies have illustrated the impact of early life trauma (ELT) and adult onset PTSD on affective executive control. We aimed at examining the interaction between a history of ELT and current PTSD diagnosis on performance on an affective executive control task and white matter integrity.
Methods: 225 Veterans from TRACTS of the VABHS were grouped for current PTSD diagnosis (PTSD+ = 134 / PTSD- = 91) and for a history of ELT (ELT+ = 65, ELT- = 160). All subjects performed the Affective Go/No-Go task of the CANTAB and errors, as well as reaction time, were the variables of interest. Participants also underwent a diffusion-tensor imaging scan.
Results: There was no significant interaction between ELT and PTSD on AGN. ELT+ subjects showed a significantly greater number of errors on the AGN [F (1,219) = 8.46, p. < .004]. There was no main effect of ELT on FA, however there was a significant interaction (p. <.05, corrected) between ELT and reaction time on FA for both positive (widespread clusters) and negative targets (left cingulate bundle).
Conclusions: PTSD diagnosis is not associated with impaired performance in our study, though individuals with a history of ELT showed greater number of errors across both positive and negative valence. The interaction between FA and reaction time in the ELT group suggests altered neurodevelopmental trajectories leading to potential deficits in behavior. This may constitute a risk factor for later psychopathology.

Keywords: PTSD, White Matter, Affective Processing, Veterans, Childhood Trauma
Supported by: B9254-C

135. Unilateral Convergent Validity Between fMRI Paradigms Assessing Response to Threat

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Background: Responses to threat are often used as probes of amygdala (AMG) functioning in affective neuroscience studies1. However, it is difficult to compare results across studies due to the use of different paradigms. Two widely used paradigms assess response to threat while viewing emotional facial expressions or negatively valence pictures. We aimed to test whether AMG BOLD responses in these paradigms show convergent validity, or if paradigm selection influences AMG engagement.
Methods: 20 healthy participants (11 males, 21.8±3.6y.o.) completed two fMRI tasks: one involved the matching emotional faces paradigm2, the other involved viewing cued aversive pictures (CAP)3. Preprocessing and first-level analyses (SPM8) contrasted aversive conditions against their control condition and baseline (threshold=punc<0.001). Group level results were masked with bilateral AMG images. Marsbar was used to extract percent signal change (%SC).

Results: rAMG (ke=63;pFWE=0.000;[24,-7,-17]) and lAMG (ke=62;pFWE=0.000;[-24,-7,-17]) were recruited when viewing CAP compared to baseline; %SC correlated between both AMG (r=0.546, p=0.013). rAMG (ke=57;pFWE=0.000;[21,-4,-17]) and lAMG (ke=52;pFWE=0.000;[-27,-4,-20]) were recruited when matching negative facial emotions compared to shapes; %SC correlated between both AMG(r=0.658,p=0.002). Only %SC in rAMG showed association between paradigms (r=0.616,p=0.004).
Conclusions: Both tasks successfully engaged bilateral AMG, although the contrasts for such recruitment differed qualitatively. Signal in the rAMG showed a robust association between tasks, suggesting a shared functionality (threat response) and convergent validity between tasks for the rAMG. By contrast, the lack of correlation between lAMG responses suggests independent and differential processing across paradigms, and that different threat probes of lAMG functioning will show divergent patterns of behavioral correlates.

Keywords: Amygdala, fMRI, Threat Response, IAPS, Facial Emotion
Supported by: NIMH 5R01MH098098

136. Regulating Negative Affect: A Neurophysiological Investigation of Self-Generated and Externally-Provided Reappraisal

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Background: The late positive potential (LPP) is an event-related potential (ERP) component that is larger for emotional compared to neutral stimuli and is sensitive to emotion regulation strategies, such as cognitive reappraisal, which involves re-interpreting a negative stimulus in order to make it less negative. Similarly, if participants are provided with a reappraisal, such as hearing a neutral description prior to viewing a negative image, rather than self-generated, negative affect ratings and LPP magnitude to the image are also reduced. Together, these findings suggest that both reappraisal strategies are effective at modulating affect and neural activity. However, no studies have directly compared these two reappraisal strategies to determine if they effect negative affect and/or LPP magnitude similarly and whether reappraisal modifies responses to subsequent encounters with stimuli.
Methods: We conducted an ERP study in healthy adult volunteers (n = 26) and measured LPP magnitude and negative affect to negative images during two phases. The emotion regulation phase involved two different reappraisal strategies, self-generated and externally-provided. During the re-exposure phase, the same images were passively viewed.
Results: During reappraisal, neither reappraisal strategy (reappraise/neutral description) had an effect on the LPP. However, both reappraisal strategies did significantly reduce negative affect ratings. During the re-exposure phase, regardless of strategy, images that were previously reappraised had increased LPP amplitude compared to negative images that were not reappraised. Moreover, both reappraisal strategies had a sustained effect on negative affect ratings.
Conclusions: Reappraisal of negative affect can down-regulate negative affect not only in the moment, but also on subsequent encounters with stimuli regardless of self-generated or externally-provided reappraisal.

Keywords: reappraisal, emotion, late positive potential, event related potential

137. Abnormal Pain Amplification During an Experimental Pain Inhibition Procedure in Chronic Widespread Pain Patients

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Background: Fibromyalgia is a chronic widespread pain disorder of unknown etiology. Recently, our group has repeatedly shown that fibromyalgia is associated with a deficit in inhibitory conditioned pain modulation (ICPM). We also observed high heterogeneity from one patient to another, raising the possibility that a sizeable sub-group of fibromyalgia patients may actually report pain amplification during the elicitation of ICPM systems in experimental settings. The objective of the current experimental study was to quantify the rate of fibromyalgia patients reporting abnormal pain amplification in such circumstances.
Methods: Participants were 153 fibromyalgia patients and 157 healthy controls. Thermal stimuli were used to measure pain thresholds. Pain inhibition was elicited using a tonic thermal test (Peltier thermode) administered before and after activation of ICPM mechanisms by means of a cold-pressor test (CPT).
Results: Thermal pain thresholds were lower in fibromyalgia patients compared to healthy controls. Pain ratings during the CPT were higher in fibromyalgia patients, relative to controls. In addition, ICPM efficacy was weaker in fibromyalgia patients compared to controls. Finally, the rate of fibromyalgia patients who reported pain amplification during the ICPM procedure was significantly increased compared to that of controls (49% versus 14%; $p<0.05$).
Conclusions: These results further confirm that fibromyalgia is not only associated with thermal hyper-algesia and deficient ICPM systems, they also reveal that a large proportion of these patients experience pain exacerbation in circumstances where they should normally experience pain relief. These results show that the functioning of ICPM mechanisms is clearly abnormal in fibromyalgia.

Keywords: Chronic widespread pain, Pain inhibition, Pain amplification, Psychophysics
Supported by: Instituts Servier

138. Changes in Fear Learning and Extinction Following Controlled Cortical Impact and Single Prolonged Stress in Rats

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Background: Mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD) are debilitating conditions that often occur together following traumatic events. Changes in fear-associated learning have been found in rodent models of PTSD and mTBI,

and in PTSD patients. However, limited work has explored changes in fear-associated learning following both PTSD and mTBI. In this study, we explored the effect of controlled cortical impact (CCI) and single prolonged stress (SPS), models of mTBI and PTSD, on fear-associated learning and extinction in rodents.
Methods: 24 Sprague-Dawley rats underwent CCI (5 mm impact, 1.5 mm depth, 3.0 m/s velocity, 100 ms dwell time). An additional 24 rats received craniotomies without receiving impact. Seven days after CCI or sham, 12 rats from each group underwent SPS, while another 12 rats from each group remained in their cages. Seven days later, all rats underwent a 3-day fear learning and extinction paradigm in individual observation chambers. Freezing during the extinction recall phase was scored and analyzed.
Results: There was no difference in baseline freezing between the groups. Three-way repeated measures ANOVA (time x injury x SPS) found no significant effect of injury or SPS, but there was an interaction approaching significance between freezing, injury and SPS in the CCI group ($F(2,84)=2.805$, $p=.066$).
Conclusions: These results suggest that there may be an effect of SPS on fear extinction retention following brain injury in rodents. Immunohistochemistry will characterize the inflammation and damage following the injury, and analysis of the fear acquisition and extinction phases will further elucidate the effect of mTBI and PTSD together on fear learning.

Keywords: mTBI, PTSD, Fear, Learning
Supported by: Private donor

139. Increased Histone Acetylation Enhances Contextual Fear in Sign-Tracking Rats, but not in Goal-Trackers

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Background: Individual differences in appetitive Pavlovian conditioned approach (PCA) behavior predict conditioned fear responses in rats. "Sign-trackers" (STs) reliably approach conditioned reward cues and are less sensitive to contextual fear conditioning than "goal-trackers" (GTs), who simply use conditioned cues as predictors and approach the location of the impending reward delivery. Epigenetic modifications of DNA are critical for the consolidation of contextually conditioned fear. However, it is unknown whether variation in experience-dependent epigenetic modulation contributes to individual differences in the expression of contextually conditioned fear. We sought to determine whether experimental manipulation of histone acetylation differentially affects contextual fear conditioning in STs vs. GTs.
Methods: 48 Sprague-Dawley rats were characterized as STs and GTs using a PCA procedure in which a retractable lever served as a cue or "sign" predicting delivery of a food reward. Following PCA training, 200 mg/kg of the histone deacetylase inhibitor sodium butyrate was administered intraperitoneally one hour prior to contextual fear conditioning. The following day, freezing behavior was measured as an index of conditioned fear to the context.
Results: During the expression test, conditioned freezing to the context was significantly lower among STs than GTs. Sodium butyrate increased contextual fear expression in STs, but not in GTs.
Conclusions: These findings suggest that individual differences in contextual fear conditioning may be mediated by individual differences in experience-dependent epigenetic modulation of gene expression. Further characterization of these mechanisms may lead to novel therapeutic targets for experience-dependent psychopathologies, such as addiction and post-traumatic stress disorder.

Keywords: Pavlovian conditioning, autoshaping, epigenetic, individual differences, anxiety
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140. Interrelated Functional and Structural Amygdala Plasticity Following Internet-delivered Cognitive Behavior Therapy for Social Anxiety Disorder

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Background: Functional magnetic resonance imaging studies have consistently showed increased amygdala responsiveness in Social Anxiety Disorder (SAD), which decreases after anxiolytic treatment (e.g., Cognitive Behavior Therapy, CBT). However, less is known about treatment-related structural gray matter (GM) volume changes. Furthermore, the relationship between functional and structural plasticity are largely neglected in the literature.
Methods: Functional and structural neuroimaging were used to assess 26 SAD patients. The patients were randomized to receive Internet-delivered CBT (ICBT), or a control condition. The Clinical Global Impression-Improvement scale (CGI-I) determined clinical response. Also, we assessed level of anticipatory speech anxiety. At pre-, and post-treatment, blood-oxygen-level dependent (BOLD) responses to self-referential criticism were recorded, and structural data was examined with voxel-based morphometry (VBM).
Results: CGI-I assessment showed that eight (61%) patients were deemed as responders following ICBT, and 3 (23%) in the control group ($Chi\text{-}2=3.90$, $p=0.047$). Time x treatment interactions showed decreased amygdala BOLD response ($Z=3.28$, $p=0.015$, Family Wise-Error corrected, FWE), and amygdala GM volume ($Z=3.30$, $pFWE=0.024$) after ICBT. At baseline, GM amygdala volume was correlated with anticipatory anxiety ($Z=2.96$, $pFWE=0.040$), and amygdala GM atrophy following ICBT was correlated with decreased anticipatory anxiety ($Z>2.83$, $pFWE<0.055$). Moreover, the amygdala BOLD response change was associated with the local GM atrophy after ICBT ($Z>2.45$, $pFWE<0.029$).
Conclusions: This is the first randomized study to evaluate multiple imaging modalities and the brain´s plasticity to an anxiolytic treatment. The functional and structural plasticity was highly correlated as indicated by anxiety-related BOLD signal change and GM volume in the amygdala following ICBT.

Keywords: fMRI, Social Anxiety Disorder, Voxel-based Morphometry, Amygdala, Cognitive Behavior Therapy

141. Functional Uncoupling of a Single NMDA Subunit in the Prefrontal Cortex Protects Against Behavioral Dysfunction After Early Life Stress

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Background: Early life stress (ELS) exposure increases vulnerability to psychiatric disorders, including depression and anxiety, which often first emerge in adolescence. Growing evidence implicates aberrant development of the prefrontal cortex (PFC) in ELS effects. We recently reported that maternal separation ELS causes overexpression of the NMDA subunit NR2A in PFC of male adolescents. Here, we aimed to determine whether manipulation of PFC NR2A could prevent ELS-induced anxiety in adolescence.
Methods: Male rat pups were maternally separated for 4hrs/day between postnatal days (P)2-20. On P28, subjects (n=8) were implanted with cannulae aimed at the medial PFC. TAT2A (100 μM or 500 μM) or control peptide microinjections were performed every alternate day between P31-40. At P41 subjects were tested in the elevated plus maze (EPM). The following day, subjects were tested for novelty-induced locomotion. A separate cohort (n=3) were microinjected with TAT2A or control peptide and sacrificed on P40 to confirm uncoupling of NR2A.
Results: ELS resulted in significantly more anxiety-like behavior in the EPM, evidenced by less time spent in the open arms (main effect of Group: $F[1,35]=19.73$, $p<0.0001$). Subjects administered 500 μM TAT2A were protected from ELS-induced anxiety-like behavior ($F[2,35]=4.76$; $p=0.015$). TAT2A did not protect subjects from increased novelty-induced activity after ELS (Main effect of Group: $F[1,39]=4.71$, $p=0.036$). Immunoprecipitation revealed that TAT2A successfully uncoupled NR2A from the postsynaptic density within the PFC.
Conclusions: These data suggest that elevated NR2A activity and subsequent NMDA dysfunction in the PFC is a biological substrate of ELS-attributable anxiety, but not ELS-attributable changes in response to novelty.

Keywords: maternal separation, adolescence, NMDA, anxiety
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142. Maternal Separation Increases IBA-1 Expression: A Microglia Activation Marker in the Prefrontal Cortex of Adolescent Males Following a Second Hit of Stress

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Background: Early life stress (ELS) increases susceptibility for psychiatric disorders that emerge in adolescence. Growing evidence implicates aberrant development of the prefrontal cortex (PFC), as well as increased pro-inflammatory activity, in ELS-attributable disorders. However, the mechanism by which neuroinflammation in the PFC is associated with ELS effects is unknown. A major source of neuroinflammation is via resident microglia. Early life immune activation or adult stress exposure can cause an enduring sensitized microglial phenotype and exaggerated inflammatory responses to subsequent stimuli. Here, we explored whether ELS promotes sensitization of PFC microglia to a chronic mild stressor in adolescence.
Methods: Male and female rats were maternally separated (ELS; n=15-17/group) or left in their home cage between postnatal days 2-20. From P39-54, animals either underwent chronic food restriction (FDR; to 90% body weight) or were left undisturbed. At P55 brains were processed for immunohistochemistry towards IBA-1, a microglia marker that is up-regulated in sensitized microglia.
Results: An interaction between rearing condition and adolescent stress condition was found in males ($F[1,31]=4.321$; $p=.046$). ELS-exposed males that were also subjected to FDR in adolescence displayed heightened Iba-1 in the PFC; Iba-1 was not elevated in non-stressed ELS subjects. Interestingly, female microglial activity was unaffected by either rearing condition or adolescent stress condition.
Conclusions: These data suggest that there are sex differences in the developmental trajectory and mediators of ELS effects on microglia. ELS may promote microglial sensitization in males, which could prime microglia toward an exacerbated neuroinflammatory response to stress during adolescence.

Keywords: maternal separation, adolescence, stress, microglia
Supported by: 1R21MH097182-01A1

143. Disruption of Amygdalar Functional Connectivity in PCDH10 Haploinsufficient Mice (Pcdh10+/-)

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Background: Activity in the amygdala is thought to mediate social learning and abnormalities in this brain region have been implicated in Autism Spectrum Disorders (ASD). While the anatomical connectivity of the amygdala has been well studied, its functional connectivity has not. This study investigated amygdalar connectivity in mice lacking one copy of protocadherin 10 (*PCDH10)*, an ASD associated gene. Protocadherin 10 is a cell adhesion protein involved in neural circuit formation and its expression is enriched in the basolateral amygdala (BLA).
Methods: Coronal brain slices from 30-day-old $Pcdh10^{+/-}$ and wild-type littermates were treated with voltage sensitive dye and imaged at 1kHz. Following lateral amygdala (LA) stimulations, strong responses were observed in the neighboring BLA and striatal regions. This strong striatal response was delayed by 2 to 3 msec, consistent with monosynaptic responses to LA stimulation. To test whether this synaptic connection propagated high-frequency oscillations, gamma-band bursts were produced in the LA. The latter generated both sustained and high frequency ensemble activity in the striatum and BLA.
Results: There were no significant differences in EPSP size in the BLA and striatum between genotypes, but $Pcdh^{+/-}$ mice had significantly less gamma-band power in the BLA than wild types. Differences in power were not observed in the striatum.
Conclusions: The fact that EPSP responses in $Pcdh^{+/-}$ and wild-types were similar but that $Pcdh^{+/-}$ displayed a significant reduction of gamma-band power in the BLA suggests a local circuit disruption in the BLA of these haploinsufficient mice. These findings provide evidence of potential circuit abnormalities in ASD.

Keywords: Autism, Amygdala, Voltage Sensitive Dye Imaging, Electrophysiology, Protocadherin-10
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144. The Orbitofrontal Cortex Regulates Behavioral Flexibility in Both Appetitive and Aversive Domains

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Background: The orbitofrontal cortex (OFC) encodes changes in the predictive relationship between a stimulus and an outcome, but less is known about its role in detecting changes in *response*-outcome associative contingencies. Furthermore, the majority of OFC literature in rodents has focused on appetitive conditioning tasks—little is known about its role in processing aversive outcomes, despite abundant evidence from human imaging literature implicating the OFC in fear extinction. We suggest that the OFC is necessary for behavioral flexibility in both appetitive and aversive domains as measured by *1)* response-outcome contingency degradation and *2)* extinction of conditioned fear.
Methods: CaMKII-driven Gi-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) were expressed bilaterally in the OFC. Mice were then trained to generate two food-reinforced responses. Next, the likelihood that one response would be reinforced was reduced, followed immediately by administration of the DREADD-activating ligand Clozapine-N-oxide (CNO). A probe test conducted 24 hours later was used to determine whether mice expressed goal-directed, or habitual, response strategies. Subsequently, mice were subjected to Pavlovian fear conditioning, and CNO was administered in conjunction with extinction training. Extinction retention tests were conducted in the absence of further CNO treatment.
Results: Gi-DREADD activation following response-outcome contingency degradation obstructed goal-directed decision-making (p=0.03). Moreover, activation during fear extinction training prevented extinction retention (p=0.01). Single cell recordings from OFC neurons indicated that Gi-DREADD activation exerted its effects by attenuating LTP induction.
Conclusions: LTP in the OFC is necessary for stable encoding of outcome-based conditioning in both appetitive and aversive domains.

Keywords: Orbitofrontal, Decision-making, Fear, DREADDs, LTP
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145. Lesions of the Orbitofrontal Cortex Impair Model-based Learning in a Rodent Multi-Stage Decision Making Task

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Background: Disruptions in the balance between model-free (MF) and model-based (MB) reinforcement learning strategies may contribute to the cognitive impairments observed in individuals with psychiatric disorders. Here, we developed a rodent version of a multi-stage decision-making (MSDM) task to determine the role of the orbitofrontal cortex (OFC) in MF and MB learning strategies.
Methods: 12 male rats received lesions of OFC or sham surgery and were trained on a MSDM task analogous to that used in humans. In this task, rats made decisions between two options in each of two successive trial stages: in the first stage, rats chose between two levers leading to either a common or rare transition to a second stage where two noseports were illuminated. Entries into illuminated noseports were probabilistically reinforced.
Results: The probability that rats would stay on the first-stage option based on the trial outcome (win/lose) and trial type (common/rare) was calculated. Analysis of the trial outcome x trial type x lesion interaction (p=0.04) indicated that sham rats displayed evidence of MB learning (trial outcome by trial type interaction: p=0.01), while lesion rats only displayed evidence of MF learning (trial outcome: p=0.002).
Conclusions: These data indicate that rats use both MF and MB strategies to guide their decision-making processes and that the OFC plays a critical role in MB learning. Because the OFC is altered in many psychiatric disorders, our results suggest that OFC dysfunction of MB learning may underlie the cognitive impairments observed in psychiatric disorders.

Keywords: Reinforcement learning, orbitofrontal cortex, model-based learning, cognition
Supported by: DA011717; DA027844; 5T32 MH14276

146. Effects of Glucocorticoids and Oxidative Stress on Monoamine Oxidase A (MAO-A) Activity in the Prefrontal Cortex in Rodents: Implications for Major Depressive Disorder (MDD)

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Background: MAO-A is an enzyme in the brain that metabolizes monoamines, creates oxidative stress, and participates in apoptosis. Greater MAO-A level, particularly in the prefrontal and anterior cingulate cortices (PFC, ACC), is associated with major depressive episodes (MDEs) and high risk states. MAO-A levels are typically highly correlated with MAO-A activity. Understanding the effects of environmental influences on MAO-A activity may lead to novel treatment strategies. This study examined the effects of (1) treatment with the synthetic glucocorticoid dexamethasone (DEX) and (2) depletion of the antioxidant glutathione (GSH) with diethyl maleate (DEM) on MAO-A activity in the rat PFC and ACC.
Methods: (1) Sprague-Dawley rats received either vehicle, 0.05mg/kg/day, 0.5mg/kg/day, or 2.0mg/kg/day DEX for 8 days by osmotic minipumps (n=7-10/group). (2) Sprague-Dawley rats received either vehicle for 3 days, vehicle for 2 days and 5mmol/kg DEM for 1 day, or 5mmol/kg DEM for 3 days i.p. (n=11-12/group). MAO-A activity in homogenates was measured using fluorescence spectrophotometry.
Results: (1) DEX treatment dose-dependently increased MAO-A activity in the PFC (p<0.0001) and ACC (p=0.01). (2) DEM treatment increased MAO-A activity in the PFC (p=0.04) and showed a trend in the ACC (p=0.10).

Conclusions: This is the first study to demonstrate that glucocorticoid administration elevates MAO-A activity in young adult rodents and the first study to demonstrate that GSH depletion increases MAO-A activity in the rat PFC. Reducing glucocorticoid agonism and increasing GSH may be potential strategies to reduce MAO-A activity in MDEs, given that MAO inhibitors are not always feasible in clinical treatment.

Keywords: Monoamine Oxidase A (MAO-A), Dexamethasone, Glutathione Depletion, Prefrontal Cortex, Major Depressive Disorder
Supported by: Canada Research Chair

147. A Novel Pre-clinical Model of Cancer-Induced Depression

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Background: Nearly 42% of cancer inpatients develop depression, compared with 8-12% of the general population. In addition to the psychosocial impact of a cancer diagnosis, biological mechanisms may be involved, with evidence suggesting that depression symptoms precede cancer diagnosis. This study aims to establish the first pre-clinical model of cancer-induced depression (CID).
Methods: 51 BALB/c mice were randomized to 4 groups. The positive control (PC; n=12) and reversal (n=12) mice received 35ug/mL of oral corticosterone for 21 days to induce depressive behaviours. Reversal mice received 150ug/mL of fluoxetine (FLX) for an additional 21 days. Cancer mice (n=15) received subcutaneous injections of 4T1 mammary carcinoma cells. Negative control (NC; n=12) mice received sham injections. The sucrose preference test (SPT) was used to test for anhedonia, and the forced swim test (FST) was used to test for behavioural despair. Data was analyzed using one-way ANOVA with Tukey's correction for multiple comparisons.
Results: PC mice had reduced sucrose preference on the SPT and increased immobility time on the FST compared to control (SPT: 58.5±3.3% vs. 70.2±2.1%, $p<0.05$; FST: 233.8±23.1s vs. 191.2±31.5s, $p<0.01$). Reversal mice had intermediate sucrose preference (64.5±3.2%, n.s.) and decreased immobility compared to PC (190.4±42.7s vs. 233.8±23.1s, $p<0.01$). Cancer mice had decreased sucrose preference and increased immobility compared to NC (SPT: 60.4±3.35% vs. 70.2±2.1%, $p<0.05$; FST: 227.7±30.7s vs. 191.2±31.5s, $p<0.01$).
Conclusions: Detection of depressive behaviours in the PC group, and reversal of these behaviours by FLX establish the validity of the SPT and FST. Using these tests, the proposed CID model demonstrated depressive behaviours. This model opens new avenues of investigation into CID mechanisms and novel drug targets.

Keywords: Depression, Cancer, Mouse Model
Supported by: Juravinski Cancer Centre Foundation

148. Altered Dopamine Receptor Density and Impaired Transient Dopamine Efflux in Nucleus Accumbens of Antidepressant-Resistant Rats

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Background: Antidepressant-resistance remains a significant burden in the treatment of depression but the underlying pathology is unclear. We, and others have demonstrated that chronic treatment with adrenocorticotropic hormone (ACTH) can induce a state of tricyclic antidepressant-resistance in rodents. The present study aimed to evaluate the mesolimbic dopamine pathway as an alternative therapeutic target in this preclinical model.
Methods: Fast-scan cyclic voltammetry was used to quantify electrically-evoked phasic dopamine efflux in the nucleus accumbens (NAc) of urethane-anesthetized rats pre-treated with 100 µg/day of ACTH or vehicle for 14 days. Autoradiographic binding for D1-like receptors (D1R), D2-like receptors (D2R) and dopamine transporter (DAT) in the NAc was evaluated using [3H]SCH-23390, [3H]YM-09151-2 and [3H]GBR-12935, respectively. The antidepressant action of bupropion (20 mg/kg, i.p.), which functionally enhances transient dopamine efflux through reuptake blockade, was also evaluated in this model utilising forced swim test.
Results: Stimulation-evoked (23 pulses, 60 Hz, 125 µA) NAc transient dopamine efflux was significantly attenuated in ACTH-treated animals relative to controls, an effect restored with selective DAT blockade (GBR-12909 10 mg/kg). In ACTH-treated animals D2R and D1R binding density in the NAc core and shell was upregulated, although NAc DAT binding density was not significantly altered. Finally, bupropion treatment significantly reduced immobility in the forced swim test for both control and ACTH treated animals.
Conclusions: Taken together, these data show reduced transient dopamine signalling associated with antidepressant-resistance following chronic ACTH treatment. This reduced dopamine signalling may lead to compensatory upregulation of D1R and D2R. Improving dopamine efflux generated antidepressant-like effects in this model.

Keywords: dopamine, treatment-resistant depression (TRD), animal model, antidepressant, adrenocorticotropic hormone (ACTH)
Supported by: State of Minnesota

149. Effects of CNS Region-specific versus Peripheral Increased TNF on Emotional Behaviour in Mice

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Background: Comorbidity of MDD (major depressive disorder) and autoimmune disorders supports the growing evidence that the pro-inflammatory cytokine tumor necrosis factor alpha (TNF) might play an important role in the aetio-pathophysiology of MDD.
Methods: In mice, the effects of brain-region specific or peripheral increase in murine TNF on MDD-relevant emotional behaviours were investigated using auditory-CS fear conditioning. Central expression of TNF was increased by bilateral injection of an adeno-associated (AAV) murine TNF vector in a specific brain region. After 14 days of viral expression, a localized, dose-dependent increase in TNF protein to 0.5-100 pg/mg tissue protein vs <0.3 pg/mg in control mice was observed, in the absence of effects on brain cytoarchitecture or peripheral TNF levels. When murine TNF was injected daily at 1µg i.p for 6 days, plasma TNF level was 600 pg/ml after 1 h (0.6 pg/ml in controls) and declined rapidly. In brain, TNF level in amygdala was 2.7 pg/mg tissue protein (2.5 pg/mg in control mice). When murine TNF was administered continuously via subcutaneous osmotic minipump at 0.5 µg/day for 7 days, plasma TNF was 35 pg/ml at day 1 and 8.6 pg/ml at day 3 (0.5 pg/ml in controls).
Results: Amygdalar viral TNF expression was without effects on fear conditioning/expression. When murine TNF was injected at 1µg i.p., fear expression was increased ($p<0.03$). When murine TNF was administered continuously via subcutaneous osmotic minipump at 0.5 µg/day, fear conditioning/expression were unaffected.
Conclusions: Integrating the current findings indicates that increased TNF exerts important indirect but not direct effects on the neurobiology underlying emotional responses in mice.

Keywords: Depression, Mouse model, Fear Conditioning, TNF
Supported by: Swiss National Science Foundation (SNF)

150. Lateral Habenula Deep Brain Stimulation in an Animal Model of Antidepressant Resistance: A Role for CaMKII, GSK3 and AMPK in Stress Response

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Background: Neuromodulation of the associated cortico-limbic circuitry effectively reduces symptoms of depression in severely treatment-resistant individuals. The lateral habenula (LHb) is a neurosurgical target of clinical interest for deep brain stimulation (DBS) treatment of refractory depression. Yet, the underlying mechanisms whereby LHb stimulation brings about treatment response remains unclear.
Method: This study investigated the antidepressant actions of high frequency LHb DBS (130 Hz; 100µA; 90µSec) in an animal model of antidepressant resistance induced by a chronic administration of adrenocorticotropic (ACTH) hormone. The efficacy of DBS was assessed by its capacity to reduce immobility time in the forced swim test (FST). Treatment groups comprised of ACTH DBS (n =7), ACTH sham-surgery animals (4 screws placement; n =8), ACTH (n =7) and Saline controls (n =8).
Results: High frequency LHb DBS significantly reduced immobility in ACTH-treated animals (n = 7; $p < 0.05$) and some attenuation of this behavior was also observed in those with sham-surgery. Western blot results suggest changes in CaMKIIα, βCaMKII, GSK3β and AMPK in the LHb region following DBS, where it was correlated with immobility time. Furthermore, p-βCaMKII, p-GSK3β and p-AMPK was positively associated with passive behavior in the infralimbic and nucleus accumbens regions.
Conclusions: The findings herein suggest that DBS of the LHb has antidepressant actions in the ACTH-induced animal model. Importantly, protein expressions involved in synaptic plasticity, apoptotic activation and energy metabolism were associated with animals' behavioral response to stress. The specific role of the LHb and DBS therapeutics in regulating depression circuitry in treatment resistance warrants further investigation.

Keywords: deep brain stimulation, lateral habenula, antidepressant action, animal model, adrenocorticotropic hormone (ACTH)
Supported by: State of MN

151. Propranolol Rescues the Outcome of Posttraumatic Stress Disorder (PTSD)-like Event via Modulating the Stability of Surface GluR1 in the Lateral Amygdala (LA) of Rat

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Background: PTSD is a psychotic disorder featured with enhanced retention of fear memory and accompanied by increased norepinephrine level in CNS. Propranolol is a β-adrenoreceptors antagonist and has been widely used in clinic for the treatment of PTSD, but the underlying mechanism remains to be elucidated.
Methods: PTSD were mimicked by fear conditioning model. Electrophysiological recording and molecular biological technique were used to explore the mechanisms of propranolol.
Results: 1. Reactivation of cue-fear memory increased norepinephrine level in LA ($F(1, 6)=6.54$, $P=0.043$). 2. Both exogenous norepinephrine and fear reactivation impaired LA-LTD, promoted surface delivery of GluR1 in LA. 3. Propranolol (5 and 10 mg/kg) intraperitoneal injection attenuated the reactivation-induced strengthening of fear memory retention ($F(2, 21)=10.9$, $P=0.001$), GluR1 surface expression and impairment of LA-LTD ($F(3, 39)=42.20$, $P<0.001$). Similar effects caused by exogenous norepinephrine also could be suppressed by propranolol. 4. Intra-amygdala infusion of propranolol (1 µg per site) attenuated reactivation-induced GluR1 surface expression, impairment of LTD and enhanced fear memory retention in rats ($F(1, 14)=78.10$, $P<0.001$).(Fig1 A-D) 5. Overexpression of C terminal tail of GluR1 (GluR1-C-tail) in LA of rats, which blocked the phosphorylation and surface trafficking of GluR1, also

attenuated impairment of LTD from 91.86±5.48% to 72.45±3.01% (F(1, 13)=10.33, P=0.007) and enhanced fear memory retention (F(1, 15)=95.72, P<0.001).(Fig1 E-I)

Conclusions: These findings uncover new mechanisms for therapeutic effect of propranolol on PTSD, which involve modulating the stability of surface GluR1 in LA.

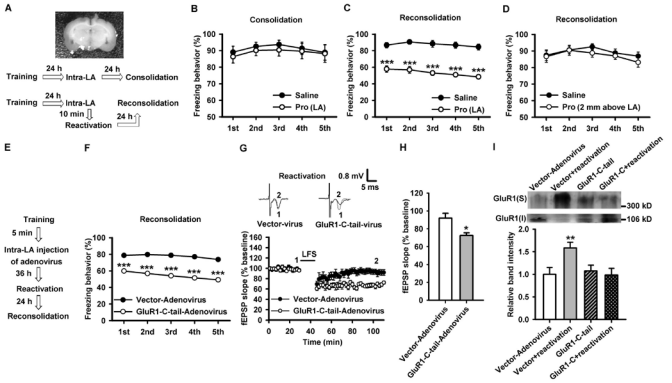

Fig1. Antagonizing β-AR or blocking GluR1-C terminal phosphorylation attenuates reactivation-induced LA-LTD impairment and fear memory retention. A-D, Intra-LA but not 2 mm above LA infusion of propranolol significantly attenuated fear memory retention. E-I, Overexpression of GluR1-C-tail in LA suppressed the reactivation-induced fear retention, recovered impairment of LA-LTD.

Keywords: PTSD, propranolol, amygdala, norepinephrine, LTD

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152. Influence of Reproductive Hormones and Nighttime Hot Flashes on Mood in Depressed Perimenopausal Women

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Background: The perimenopause is a period of increased risk for depression. Estradiol variability and hot flashes (HF) each increase the risk for depression during this time period. However, the relative contribution of these factors to depressive symptom severity in depressed perimenopausal women is not well understood. We hypothesized that estradiol variability and nighttime HF would independently predict worse mood in depressed perimenopausal women.

Methods: Perimenopausal women with mild depression (Montgomery-Asberg Depression Rating Scale [MADRS] score 10-24) completed assessments of mood, HF, serum estradiol and progesterone weekly for 9 weeks. Repeated-measure regression was used to examine independent associations of the coefficient of variability in estradiol, the number of progesterone elevations, and HF with mood.

Results: In 51 participants with a mean age of 48.2yrs and a baseline MADRS of 15.4, 84% reported HF. During the study period, 90% had variable but detectable estradiol levels while 10% were persistently hypo-estrogenic. In adjusted models, MADRS scores were lower in women with episodic progesterone elevation (p<0.001); greater variability in estradiol increased MADRS scores in the absence (p<0.001), but not the presence (p=0.80), of episodic progesterone elevation. Nighttime (but not daytime) HF were associated with higher MADRS scores in women with persistent hypo-estrogenism (p=0.001), but were not associated with mood in those with detectable estradiol levels (p=0.22).

Conclusions: In perimenopausal depressed women, increasing dysregulation of ovarian hormones with loss of ovulation and estradiol variability is associated with worse mood. In addition, nighttime HF are associated with worsening of mood in persistently hypo-estrogenic women.

Keywords: Estrogen/Progesterone, Depression, Perimenopause, Hot Flashes, Women

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153. Compared to Fluoxetine, Vortioxetine Promotes Earlier Increases in Dendritic Length and Spine Formation – An in vivo Study of the Hippocampal CA1 Region in the Rat Brain

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Background: Accumulating evidence suggests that depression is associated with decreased dendritic branching and spine density in cortico-limbic brain structures. Preclinical studies show that induction of long-term potentiation (LTP), a cellular correlate of neuroplasticity essential for memory and learning increases dendritic spine density. In comparison to selective serotonin reuptake inhibitors (SSRIs), the multimodal-acting antidepressant vortioxetine shows enhanced LTP and dendritic branching in rodents. We compared the effect of vortioxetine and fluoxetine on dendritic morphology in the rat hippocampus CA1 region.

Methods: Male Sprague-Dawley rats were dosed for 7 days with vortioxetine (in chow) or fluoxetine (in water) at doses producing full occupancy of the serotonin transporter. Dendritic morphology (total dendrite length, mean dendritic branch length, total number of spines, spine density, and a 3-dimensional Scholl analysis) was studied in Golgi-stained hippocampus sections. Treatment groups consisted of 12 rats, and 16 neurons were sampled per brain.

Results: Compared to untreated controls, vortioxetine-treated rats significantly increased spine number per neuron in apical and basal dendrites, as well as spine density and total dendritic length per neuron in the basal dendrites. There was no significant difference between vortioxetine-treated rats and controls with respect to the number of intersections in apical and basal dendrites. Fluoxetine-treated rats did not differ from controls on any measures.

Conclusions: Vortioxetine increased dendritic length and spine numbers at a timepoint when fluoxetine had no effect, suggesting that its mechanism of action differs from that of SSRIs.

Keywords: vortioxetine, Dendritic length, Spine formation, Hippocampus, rat
Supported by: Lundbeck

154. The Putative Bipolar Disorder Variant N543Q of the Transient Receptor Potential Melastatin 2 Channel Causes Increased Calcium Flux in Vitro

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Background: The single nucleotide polymorphism (SNP) rs1556314, N543Q in exon 11 of the Transient Receptor Potential Melastatin 2 (TRPM2) gene has been associated with bipolar disorder I in both family and case-control data sets (Xu et al., Bipolar Disorders, 2009:11:1-10). The pathophysiological relevance of this SNP in bipolar disorder is unknown. TRPM2 channels gate calcium entry into cells and the SNP is located close to the calmodulin binding region of the channel. Therefore, in the present study we investigated the effect of N543Q on calcium flux through TRPM2 channels in vitro.
Methods: Wild type (WT) and mutant N543Q human TRPM2 channels were transiently expressed in HEK293 cells and expression levels were compared by Polymerase chain reaction (PCR). Calcium uptake was measured after stimulation with the synthetic agonist Methylnitronitrosoguanidine (MNNG) in two different assays, Fluorescent Imaging Plate Reader (FLIPR) and radioactive calcium ($^{45}Ca^{2+}$) uptake.
Results: mRNA expression levels of WT and mutant TRPM2 were not significantly different. The EC_{50} for MNNG was comparable in both assays: WT EC_{50} was 1.5 mM in FLIPR and 0.82 mM in $^{45}Ca^{2+}$ uptake. Mutant EC_{50} was slightly more potent, 0.87 and 0.62 mM, respectively. In both assays, calcium flux was three-fold higher in the TRPM2 N543Q mutant compared to WT.
Conclusions: SNP N543Q close to the calmodulin binding region of TRPM2 causes an increase of calcium flux in two different assays in vitro. This gain of function could contribute to the abnormal calcium signaling hypothesized to underlie the pathophysiology of bipolar disorder.

Keywords: TRPM2, calcium uptake, bipolar disorder, MNNG, SNP
Supported by: Amgen

155. The ROCKII Inhibitor Fasudil Increases the Expression of Antidepressant-related Signaling Factors and has Antidepressant-like Efficacy in Adolescent Mice

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Background: Adolescent-onset depression is of particular concern due to increased resistance to antidepressant treatment and a high risk of recurrence that persists across the lifespan. Adolescence represents a critical period of neurodevelopment, defined by structural and synaptic maturation and reorganization within the prefrontal cortex. Although these processes are critical for the transition to adulthood, structural instability may open a window of vulnerability to neuropsychiatric disease. A drug that expedites the synaptic remodeling that occurs during adolescence may be therapeutic. To test this hypothesis, I evaluated the therapeutic-like potential of the brain-penetrant Rho-Kinase II (ROCKII) inhibitor, fasudil.
Methods: Female mice expressing thy1-derived Yellow Fluorescent Protein were administered fasudil, fluoxetine, ketamine or vehicle at postnatal day 42 (adolescence) or 90 (adulthood) prior to the forced swim test and euthanasia. Brains were frozen, and protein expression was assessed by immunoblotting, or brains were fixed for confocal fluorescence microscopy.
Results: Acute administration of fasudil had antidepressant-like properties in the forced swim test in adolescents, but not adults, and these effects were indistinguishable from those of fluoxetine and ketamine ($p<.05$ versus control). Fasudil increased expression of TrkB, p110beta (the catalytic subunit of PI3K), AKT, mTOR and PSD-95 in the adolescent medial prefrontal cortex ($p<.05$). The increase in PSD-95 was accompanied by enhanced dendritic spine pruning ($p<.05$), resulting in adult-like spine densities. At the same dose, fasudil had no effects on these signaling factors or dendritic spine density in adult mice.
Conclusions: Together these findings suggest that ROCKII inhibition may be uniquely therapeutic in the treatment of adolescent-onset depression.

Keywords: depression, adolescence, Rho-kinase, prefrontal cortex, antidepressants
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156. Molecular Mediators of State Changes in Bipolar Disorder in Human-Derived Olfactory Neurons

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Background: Neuroscience studies suggest that lithium affects molecular targets that are involved in neuronal growth, survival and maturation. But it is unclear if any of these lithium-associated molecular changes in neurons predict clinical response in bipolar disorder (BD). Here, we examined the effect of lithium-associated molecular changes human-derived olfactory neurons in clinical response.
Methods: We used human olfactory tissues obtained through nasal biopsies of healthy volunteers and of patients with BD treated with lithium carbonate for six-weeks. Combining laser capture microdissection, to avoid contamination by other non-neuronal cells, with real-time PCR, we evaluated treatment-associated transcriptional changes in 10 candidate molecules of lithium.
Results: Baseline mRNA levels for expression of GSK3β and CRMP1 are both significantly associated with BD compared to

controls (P<0.05). No difference was observed for the mRNA levels of other molecules tested, notably AKT1 and PKCε. CRMP1 is more strongly associated with reduction of depression and hypomanic symptoms (P<0.02, P<0.05) compared to the effect of GSK3β.
Conclusions: This study provides further insight into our understanding of lithium effects in bipolar disease by identifying neuronal biomarkers associated with state changes in living patients. Our study shows that lithium therapy can alter neuronal mRNA levels CRMP1 and GSK3β in vivo, and introduces CRMP1 as a potential target for new drug development for BD.

Keywords: Lithium associated molecular changes, GSK3β, CRMP1, bipolar disorder, human-derived olfactory neurons
Supported by: MH-091460; CON0001146 (Dana Foundation)

157. Olfactory Neuronal Expression of CRMP1 Is Associated with Odor and Emotional Processing

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Background: Collapsin response mediator protein 1 (CRMP1), which plays key role in axonal guidance during neurodevelopment has been associated with olfactory impairment and negative symptoms in schizophrenia. In this study, we examined if dysregulation of CRMP1 expression in human-derived olfactory neuronal tissue is related to odor identification ability and facial emotion recognition; and secondarily explored if olfactory function is correlated with emotion recognition.
Methods: Patients with bipolar disorder (BD) and healthy volunteers received psychiatric diagnostic interview, University of Pennsylvania Smell Identification Test (UPSIT), computer-based emotion recognition task (ERT), followed by nasal biopsies under local anesthesia. Laser-capture microdissection was combined with RT-PCR to study expression CRMP1 gene in the neuroepithelial layer of the biopsied tissue.
Results: CRMP1 mRNA levels were significantly associated with case/control status (P<0.05). Adjusting for bipolar disorder status, CRMP1 expression was inversely associated to total scores of UPSIT (P<0.05) and the total number of facial expressions recognized on ERT tasks (P<0.005); and directly related to the mean latency to ERT (P<0.07). Additionally, ERT score is significantly correlated to UPSIT score (r = 0.55, P<0.03).
Conclusions: The strong relationship between performance in odor tasks and emotion recognition suggests the possibility of an overlap in the neural circuitry of olfactory processing and social cognition, and further supports the relevance of CRMP1 in the integrity of these overlapping processes across disease categories.

Keywords: CRMP-1, odor processing, emotional processing, UPSIT, ERT
Supported by: MH-091460; CON0001146 (Dana Foundation)

158. Vortioxetine Promotes Maturation of Dendritic Spines- An In Vitro Study in Hippocampal Cultures

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Background: In preclinical studies, the multimodal-acting antidepressant vortioxetine enhances long-term potentiation (LTP), a cellular correlate of neuroplasticity, in hippocampal slices. However, the molecular mechanisms through which vortioxetine augments LTP remain unknown. Dendritic spines are compartmentalized, actin-rich, dynamic protrusions that are the sites of excitatory synapses. They are classified into various shapes: mushroom-shaped spines are mature, stable phenotypes, and thin or filopodia-like protrusions are immature morphologies. Since spine remodeling is implicated in plasticity and spine size dictates the strength of synaptic transmission, we assessed whether vortioxetine, relative to other antidepressants, plays a role in maintenance of dendritic spine architecture in vitro.
Methods: Hippocampal neurons were isolated from E18 rats and transfected with GFP:β-actin at 9 days in vitro (DIV). At 14 DIV, neurons were treated with vehicle, 0.5 μM vortioxetine, 2.0 μM fluoxetine, 2.0 μM duloxetine, or 2.0 μM ketamine for 1 h, a range of non-toxic concentrations shown to promote signaling in culture. Cells were colabeled with anti-GFP and anti-synapsin I. Imaging was performed using a Nikon laser-scanning confocal microscope and spine analysis with MetaMorph software.
Results: Vortioxetine, ketamine, and duloxetine induced increases in spine area, width, breadth, and length, relative to vehicle, suggesting a transition to a more mature morphology. In contrast, fluoxetine treatment promoted an increase only in length of dendritic protrusions, indicative of an immature phenotype.
Conclusions: In contrast to the SSRI fluoxetine, vortioxetine induces a mature dendritic spine phenotype. Remodeling of dendritic spines may be one mechanism through which vortioxetine can enhance synaptic transmission and plasticity.

Keywords: vortioxetine, dendritic spines, in vitro, plasticity
Supported by: H.Lundbeck A/S and Takeda Pharmacuetical Company, Ltd.

159. Bipolar Disorder GWAS Gene, Ankyrin 3, Regulates Adult Neurogenesis

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Background: Human genetic studies identified a significant association between the Ankyrin 3 gene (ANK3) and risk of bipolar disorder (BD). Abnormalities in the hippocampus are consistently linked to BD, in particular, deficits in dentate gyrus function. Our recent work has shown disruption of Ank3 in the dentate gyrus induces manic-like behaviors. As proper development of neurons in the dentate gyrus is crucial for hippocampal function, we speculated Ank3 functions in dentate gyrus neurogenesis and defects in this process may contribute to BD.

Methods: We investigated neuronal activation and adult neurogenesis in dentate gyrus of ankyrin 3 haploinsufficient mice (Ank3+/-) and wildtype littermates (Ank3+/+). Neuronal activity was evaluated by c-fos immunohistochemistry. Adult hippocampal neurogenesis was examined using stage-specific cellular markers – bromodeoxyuridine (BrdU) to label proliferating cells and doublecortin to assess maturation of newborn neurons. Furthermore, we are utilizing a novel method to regulate expression of Ank3 using the CRISPR/Cas9 system to evaluate the function of ankyrin 3 in dentate gyrus.
Results: Our unpublished studies have detected decreased c-fos expression in dentate gyrus of Ank3+/- mice while exhibiting manic-like behavior, suggesting impaired neuronal activation that may perturb hippocampal function. Altered proliferation of neural progenitor cells ($p < 0.05$) in the dentate subgranular zone and defects in neuronal maturation ($p < 0.05$) suggest impaired adult neurogenesis in the Ank3+/- animal model.
Conclusions: These data suggest Ank3 functions to regulate the development of adult-born hippocampal neurons and provide novel insight into how disruptions in neurodevelopment may underlie the pathogenesis of BD.

Keywords: Neurogenesis, Dentate Gyrus, Bipolar Disorder, Ankyrin 3, c-fos
Supported by: NIMH MH100570; NARSAD 22732; Massachusetts General Hospital Fund for Medical Discovery

160. Relative Expression of GDNF Family Receptor Alpha 1 (GFRA1) Isoforms Regulates GDNF Signaling: Implications for Depression

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Background: Neurotrophins mediate multiple aspects of neuroplasticity, and considerable evidence suggests they play a key role in the aetiology and treatment of depression. Although several reports suggest that peripheral expression of glial cell line-derived neurotrophic factor (GDNF) is reduced during depressive episodes, the regulation of central GDNF signaling in depression remains largely unexplored.
Methods: Immunoblotting and qRT-PCR were used to assess expression of GDNF signaling molecules and microRNAs in human postmortem basolateral amygdala (BLA) from depressed suicides and controls. microRNA-transfected human neural progenitor cells (NPCs) were employed to assess the upstream regulation and downstream repercussions of changes observed in human BLA samples.
Results: Analyses of human BLA revealed decreased expression of the GDNF family receptor alpha 1 (GFRA1), and increased expression of miR-511, a microRNA predicted to bind to the 3'UTR of certain GFRA1 transcripts. Transfection of NPCs with miR-511 confirmed its capacity to reduce GFRA1 protein by repressing expression of long 3'UTR-containing GFRA1 isoforms coding for the GFRA1a protein variant. GFRA1b expression, by contrast, was unaffected. Unexpectedly, knock-down of GFRA1a resulted in qualitative changes in GDNF-induced signaling, including immediate early gene and MAPK activity. In human BLA, reduced GFRA1a expression was associated with a reversal of the relationship between GFRA1 and doublecortin (DCX; a neuroplastic protein) expression.
Conclusions: microRNA-mediated knock-down of GFRA1a appears to do more than alter the gain of GDNF signaling, it may change the message. In so doing, GFRA1 a-targetting microRNAs may contribute to the decreased BLA neuroplasticity reported in depression, and could represent a strong candidate for novel antidepressant therapies.

Keywords: GDNF, Depression, Basolateral amygdala, microRNA, Neurotrophic factor signaling
Supported by: CIHR, AFSP

161. Does Plasminogen Activator Inhibitor (1,2) Mediate Depression and Cardiovascular Disease During Pregnancy? A Review of the Literature

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Background: Plasminogen Activator Inhibitor (PAI) increases coagulation by inhibiting plasmin, a protein responsible for clot degradation. Chronic dysregulation of this pathway may be implicated in the formation of atherosclerotic clots and other aspects of cardiovascular disease (CVD). Some research also proposes a link between PAI-1 and Major Depressive Disorder (MDD), suggesting a mechanism behind MDD and CVD comorbidity. This effect may be particularly evident during pregnancy because of the increased incidence of MDD and cardiovascular pathology.
Methods: Of a preliminary pool of 7765 pubmed articles, 26 were selected for inclusion into this review based upon suitability of subject matter and robustness of study.
Results: Serum PAI-1 concentration has been observed to be elevated during inflammatory cardiovascular pathologies. PAI-1 is also upregulated by pro-inflammatory cytokines. Likewise, MDD is characterized by a systemic inflammatory response. Some evidence suggests that PAI influences the conversion of pro-BDNF to mBDNF both cortically and systemically, providing a possible biochemical mechanism linking CVD and MDD. These findings have special significance in the pregnant population. A second isoform of PAI (PAI-2) is secreted from the placenta during pregnancy, further explaining the increased propensity of pregnant women to MDD and cardiovascular pathology.
Conclusions: PAI-1 and 2 mediates CVD and MDD. Further research is needed to explore this possibility and determine whether PAI may be predictive, rather than descriptive of illness. Of particular interest is the roles PAI-1 and 2 play during pregnancy, and how they may influence both MDD and CVD development in that high-risk patient population.

Keywords: Major Depressive Disorder, Cardiovascular Disease, Plasminogen Activator Inhibitor, Pregnancy

162. CD40 Agonist Antibody Induced Anhedonia In Mice Is Prevented by a TNF-Blocker but not an Indoleamine 2,3 Dioxygenase 1 Inhibitor

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Background: There is increasing evidence for comorbidity of autoimmune disorders and major depressive disorder (MDD). In autoimmunity, the CD40-CD40L pathway is essential for the response to self-antigens and leads to the synthesis of inflammatory chemo- and cytokines. In turn, several inflammatory pathways are proposed to be MDD aetiological factors, including increased tumor necrosis factor (TNF) and increased tryptophan-kynurenine metabolism via cytokine-induced Indoleamine 2,3 dioxygenase 1 (IDO1) activity.
Methods: We injected C57BL/6J mice (n=6-8/group) with a monoclonal mouse CD40 agonist antibody (CD40Ab, 10mg/kg i.p., single dose) or IgG2a control antibody. To block any TNF increase we co-injected etanercept (10mg/kg, i.p., single dose) or to inhibit IDO1 we administered an IDO1 inhibitor (onset 14 h post-CD40Ab injection, 75mg/kg per os, twice daily for 5 days).The behavioural readout consisted of a home-cage saccharin preference/consumption test. We measured TNF (flow cytometric assay) and tryptophan-kynurenine metabolites (liquid chromatography – tandem mass spectrometry) in plasma and different brain regions.
Results: CD40Ab administration reduced saccharin consumption for 7 days. In plasma, CD40Ab led to an increase in TNF (days 2-5) and an increases in plasma and brain kynurenine (Kyn) (days 2-8) and 3-hydroxykynurenine (3-HK) (days 2-6). Co-administration of etanercept prevented CD40Ab-induced reduction in saccharin consumption, whereas IDO1 inhibitor was without effect.
Conclusions: The finding that CD40Ab reduces gustatory reward sensitivity adds to the evidence that it induces sickness behaviour. High plasma TNF is essential for the CD40Ab activation of these effects. However, kynurenine pathway metabolites do not appear to be the major down-stream mediator of this pathway.

Keywords: major depression, autoimmune disorder, Tumor Necrosis Factor, Kynurenine
Supported by: Swiss National Science Foundation

163. The Immunosenescece in Early and Late Stages of Bipolar Disorder Type 1

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Background: Bipolar disorder (BD) has been associated with immunological disbalance and with accelerated aging of the immune system (immunosenescence). The present work aimed to analyze the progression of the immunesenescence process over the years of illness.
Methods: Nine BD patients with less than 5 years of ilness (early stage), 14 with more than 10 years of illness (late stage) and 21 healthy controls (HC) were enrolled in this study. Peripheral blood mononuclear cells (PBMCs) were isolated and stimulated in vitro for 0 to 3 days. The cells were immunophenotyped for immunosenesce associated subsets and read by flow cytometry.
Results: BD patients have presented a lower %Breg (H(2)=18,24; p<0,001), and lower %Treg cells (H(2)=23,53; p=<0,001) both in early and late stages. Although there was no increased percentage of CD8+CD28-CD27- in BD groups, linear regression have shown that the higher the number of manic episodes, the higher was the % CD8+CD28-CD27- (β=0,28; t=2,7; p=0,015), independently of age (β=-0,26; t=-0,618; p=0,545). After stimulation Th and Tc cell from BD patients presented a reduced proportion of the late activation marker CD71+ (F(2,38)=11,476; p<0,001) and also their Tregs reduced expression of the immunomodulatory molecule CD152 (F(2,35)=17,438, p<0,001).
Conclusions: The data concur to the hypothesis early accelerated aging, notably by reduction of B and T regulatory cells and the impaired capacity to express CD71 and CD152 in BD. The process of immunosenescence seems to be modulated not only by the years of illness but also by the number of manic episodes.

Keywords: Bipolar disorder, Immunosenescence, Inflammation, Aging, T regulatory cells
Supported by: PVEA87/2014, CAPES, FAPESP, CNPq

164. Characterization of Somatostatin Expressing Neurons in the Primate Central Extended Amygdala

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Background: The central extended amygdala contains the central nucleus of the amygdala (Ce) and the lateral bed nucleus of the stria terminalis (BSTL) and is an integral part of the neural circuit mediating fear and anxiety. Understanding the composition of extended amygdala neurons in primates is critical for understanding their complex function in relation to human behavior. The lateral Ce (CeL) and dorsal BSTL (BSTLD) regions are critical for modulating extended amygdala output and show dense soma-

tostatin (SOM) expression. We characterized these neurons in the non-human primate by examining their co-expression profiles with two neurotransmitter systems, corticotropin-releasing hormone (CRH) and dopamine, involved in modulating adaptive and maladaptive stress responses.
Methods: We used triple-labeling immunofluorescence and confocal microscopy to characterize SOM neurons in CeL and BSTLD. Specifically, we examined the neuronal co-expression of SOM with CRH as well as SOM with dopamine- and cyclic AMP-regulated phosphoprotein (DARPP-32), a marker of dopaminergic input. Cells were manually counted to determine co-localization.
Results: Consistent with prior work, we observed strong SOM stained neuropil in the CeL and BSTLD. However, SOM expressing somata comprised < 5% of the total number of neurons in these regions. Approximately 50% of the SOM expressing neurons in CeL and BSTLD also expressed CRH. In contrast we observed no SOM-DARPP-32 co-expression within CeL.
Conclusions: These studies have identified a neuronal subtype in the primate central extended amygdala that likely releases SOM and CRH, but does not receive dopaminergic input. Further studies examining the functional interactions between SOM and CRH in these regions will be important for developing new treatments for stress-related psychopathology aimed at altering specific extended amygdala functions.

Keywords: Central nucleus of the amygdala, CRH, Anxiety, Bed nucleus of the stria terminalis
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165. A Meta-analysis and Meta-regression of Immune Activation in Posttraumatic Stress Disorder

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Background: Studies have shown that Posttraumatic Stress Disorder (PTSD) is associated with diseases where immune activation plays a key role, such as coronary heart disease, atherosclerosis, and autoimmune diseases. Abnormal inflammatory markers have been reported in PTSD, but results are conflicting. We aim to meta-analyze inflammatory markers in PTSD.
Methods: We performed a meta-analysis and meta-regression of studies comparing peripheral inflammatory markers levels between PTSD patients and healthy control. We searched in five databases (Figure1).
Results: Eighteen studies with a total of 1067 participants were eligible for the analysis. Concentrations of interleukin (IL)-6 and IL-1β were significantly elevated in patients (Table). There were no significant differences for CRP, GM-CSF, IL-2, IL-4, IL-6, IL-8, IL-10, sIL-2R and TNF-α. Meta-regression analysis of IL-6 explained 52% of heterogeneity and suggested that the difference in IL-6 levels between PTSD subjects and controls does not seem to be explained by comorbidity with Major Depressive Disorder (Figure2).
Conclusions: Results suggest that PTSD is associated with a pattern of immune activation, including increased levels of IL-6 and IL-1β. This may help to explain the association among PTSD, comorbidities and aging.

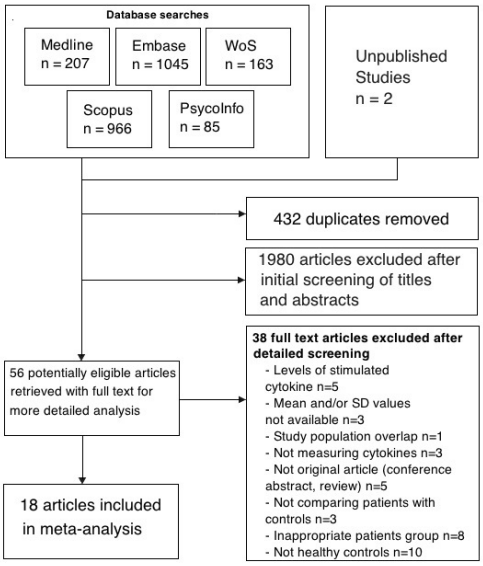

Figure 1. Flow chart describing the study selection process. WoS: Web of Science; SD: standard deviation.

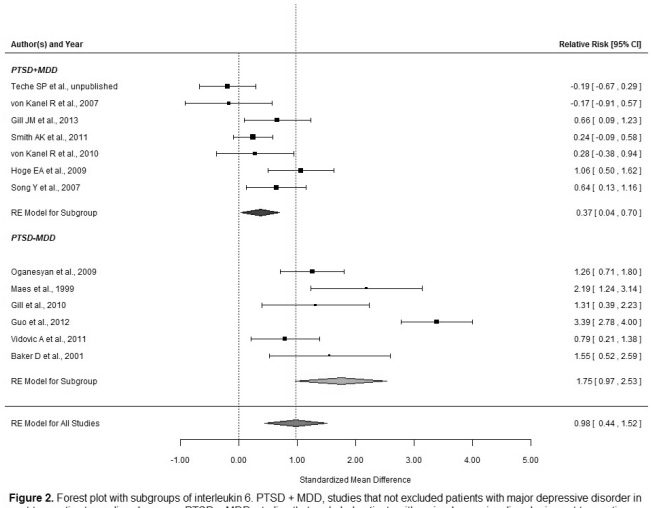

Figure 2. Forest plot with subgroups of interleukin 6. PTSD + MDD, studies that not excluded patients with major depressive disorder in post-traumatic stress disorder group; PTSD – MDD, studies that excluded patients with major depressive disorder in post-traumatic stress disorder group; RE Model, Random Effect Model.

Summary of Comparative Inflammatory Markers				
Cytokine Measured	No of Studies (No of patients/control subjects)	SMD (95% CI)	p Value	I2
IL-1β	6 (166/212)	1.622 (0.189 to 3.054)	0.026	97%
IL-2	5 (177/273)	0.077 (-1.015 to 1.169)	0.890	96.1%
IL-4	4 (139/222)	0.351 (- 0.957 to 1.659)	0.599	96.4%
IL-6	13 (332/439)	0.944 (0.425 to 1.462,)	<0.001	89.9%
IL-8	3 (112/112)	0.707 (-1.153 to 2.566;)	0.456	97.4%
IL-10	5 (172/255)	0.407 (-0.358 to 1.172;)	0.297	92%
sIL-2R	2 (77/40)	-2.645 (-7.197 to 1.906)	0.255	98.4%
TNF-α	7 (196/274)	0.398 (-0.425 to 1.221)	0.344	94.3%
CRP	4 (107/92)	-0.285 (-1.182 to 0.612)	0.533	87%
GM-CSF	2 (49/59)	-0.275 (-1.227 to 0.678)	0.572	83.3%

Keywords: Posttraumatic Stress Disorder, Meta-analysis, Major Depressive Disorder, Immune activation, Cytokine

166. Excessive Striatal Dopamine Activates Auditory Cortex Via Striato-Pallido-Thalamo-Cortical Projections in the Rat

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Background: We showed previously that infusion of dopamine into the posterior caudatoputamen in the rat selectively induces zif268 mRNA in auditory cortex in a pattern similar to that produced by sound, but not by light. Extrapyramidal motor circuits are known to comprise circuitry loops involving the anterior striatum and motor cortex. This study examined putative circuits from posterior striatum to auditory cortex using retrograde transsynaptic labeling.
Methods: Pseudorabies virus Bartha-152 expressing eGFP upon infection was unilaterally infused at stereotaxic coordinates targeting cortical layer IV of the auditory cortex. Brains from 15 rats were processed at postinoculation times every 6 h from 24-48 h. Serial sections were mounted, imaged and processed using Neurolucida. EGFP-labeled cells were quantified and brain circuits were reconstructed at different postinoculation times.
Results: Labeled circuits suggest that both ventroanterior/lateral thalamus (VA/VL) and medial geniculate (MG) were labeled first, then entopeduncular nucleus (EP), inferior colliculus (IC), subthalamic nucleus (STh), globus pallidus (GP) and caudatoputamen. Contralateral cortical labeling required initial viral spread to thalamus.
Conclusions: Retrograde labeling of auditory cortex revealed transsynaptic connections of the same caudatoputamen region in which dopamine infusion induces cortical activation. Projections from striatum to GP, STh, EP, VA/VL and auditory cortex paralleled projections from auditory brain stem to IC, MG and auditory cortex. We conclude that sequential striatal innervation of auditory cortex could provide a substrate for auditory perception unrelated to auditory sensory pathways. Thus, excessive dopamine in the "sensory" striatum could represent a trigger for a false perception of sound, or hallucination.

Keywords: hallucination, striatum, auditory cortex, transsynaptic, labeling
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167. Effects of Single Prolonged Stress: A PTSD Validated Animal Model, on Pre- and Post-Synaptic Marker Expressions in Fear-Processing Neurocircuitry

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Background: Post-traumatic stress disorder (PTSD) is a severely debilitating anxiety disorder. Core deficits of PTSD include extinction retention and contextual processing. Functionally, prefrontal cortex (PFC)-hippocampus (Hpc)- amygdalae circuitry is critical for these processes. Prolonged exposure to stress or stress hormone has been shown to lead to synaptic atrophy in lab animals. Patients with depression have also been shown to have significant decreases in synaptic arborization, synapse numbers and expression of markers of synaptic function.
Methods: To understand synaptogenesis' role in PTSD relevant fear processing of extinction recall we measured synaptogenesis markers following SPS exposure alone as well as in combination with fear learning resulting from fear conditioning, extinction and extinction recall. Synaptogenesis were measured in PTSD relevant neurocircuitry (mPFC, Hpc, and amygdala) using quantitative PCR. Within these regions, both pre- and post-synaptic signaling relevant molecules were measured: Syn1, PSD95, MAP2, GluR1 and BDNF.
Results: SPS alone significantly affected expression of BDNF and MAP2 within mPFC and the hippocampus. SPS and fear learning had a significant interaction in the expression of MAP2 and Syn1 in all three areas studied.
Conclusions: Dendritic remodeling would represent a modifiable target that could lead to viable treatments as well as furthering our understanding of etiology of this disorder. Treatment targeting dendritic remodeling is currently being investigated for multiple disorders.

Keywords: SPS, neurogenesis, PTSD, extinction
Supported by: W81XWH-08-1-0661

168. Serotonin Reuptake Inhibitor Augmentation with N-Acetylcysteine in Treatment Resistant Obsessive-Compulsive Disorder: A Double-blind Randomized Controlled Trial

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Background: N-Acetylcysteine (NAC), an anti-glutamatergic agent, is being considered as an add-on strategy for treatment-resistant obsessive-compulsive disorder (OCD). The main objective of this study was to determine if NAC is effective in treatment-resistant OCD patients after 16 weeks of serotonin reuptake inhibitors (SRI) augmentation.
Methods: Randomized, double-blind, placebo-controlled trial conducted in an OCD-specialized outpatient clinic (May 2012-October 2014). Patients were eligible if they had a DSM-IV primary diagnosis of OCD; failed to respond to at least one previous adequate pharmacological treatment for OCD; had a baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score≥ 16; and their OCD symptoms were of at least moderate severity on the Clinical Global Impression Scale. Of 145 eligible subjects, 40 (mean age=37.9 years, SD=10.9; male=52.5%; mean baseline Y-BOCS score=25.3, SD=3.9; mean number of previous adequate treatments=3.4, SD=2.0) were randomized (NAC up to 3000 mg/d, n=18; placebo, n= 22) and 35 completed
the trial. The medications that were in use at the time of randomization were maintained at the same dose. Independent assessments were conducted at baseline and at the end of the study.
Results: Both groups showed a significant reduction of the baseline Y-BOCS score at week 16, but there was no statistical difference between the two interventions (NAC=16.3%; placebo= 10.3%; F=0.17; *p value*=0.68).
Conclusions: NAC augmentation of SRI was not different from placebo in this sample of treatment-resistant OCD patients. Participant's severity profile might have influenced our results.
Trial registration: clinicaltrials.gov identifier NCT01555970

Keywords: obsessive-compulsive disorder, N-Acetylcysteine, treatment
Supported by: FAPESP

169. Baseline Blood Pressure Is Associated with PTSD Symptom Response to Prazosin in Active Duty Combat Soldiers

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Background: Prazosin, a CNS active alpha-1 adrenoreceptor (AR) antagonist, was demonstrated effective for combat trauma PTSD in a randomized controlled trial (RCT) in active duty soldiers (n=67) returned from Iraq and Afghanistan combat deployments. However, therapeutic response was variable. Because peripheral and CNS alpha-1 AR responsiveness can be estimated by standing systolic blood pressure, we hypothesized that higher standing systolic BP at BASELINE would predict therapeutic response to prazosin.
Methods: We analyzed the effects of baseline BP parameters on PTSD outcome measure responses to prazosin using linear mixed effects models.
Results: There were significantly greater reductions (greater improvement) in total CAPS score with prazosin treatment (change in slope per 10mm Hg increase in baseline standing systolic BP); (p=0.002) and similar effects on other PTSD outcome measures. Other combinations of baseline BP parameters (supine systolic, supine and standing diastolic, and orthostatic diastolic change) were similarly significant or demonstrated trends in the predicted direction. In contrast, the same analyses in placebo participants detected no signal for a baseline BP effect.
Conclusions: Higher baseline systolic BP predicts substantially greater PTSD symptom improvement with prazosin treatment. These results suggest that peripheral BP provides an indicator of increased CNS alpha-1 AR responsiveness in combat trauma PTSD. Such increased alpha-1 AR responsiveness and/or activation are the presumed target for prazosin therapeutic efficacy. Baseline BP could be a clinically useful biomarker for helping to predict the response to prazosin or other alpha-1 AR antagonist treatment in PTSD.

Keywords: PTSD, prazosin, combat, soldiers
Supported by: Department of Veterans Affairs

170. Depressed Suicide Attempters Have Smaller Hippocampus Than Depressed Patients Without Suicide Attempts

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Background: Despite known relationship between hippocampal volumes and major depressive episodes (MDE) and the increased suicidality in MDE, the links between hippocampal volumes and suicidality remain unclear in major depressive disorders (MDD). If the hippocampus could be a biomarker of suicide attempts in depression, it could be useful for prevention matters. This study assessed the association between hippocampal volumes and suicide attempts in MDD.
Methods: Hippocampal volumes assessed with automatic segmentation were compared in 63 patients with MDD, with (n=24) or without (n=39) suicide attempts. Acute (< one month) and past (> one month) suicide attempts were studied.
Results: Although not different in terms of socio-demographic, MDD and MDE clinical features, suicide attempters had lower total hippocampus volumes than non-attempters (4.61 (±1.15) cm3 vs 5.22 (±0.99) cm3; w=625.5; p=0.03), especially for acute suicide attempts (4.19 (±0.81) cm3 vs 5.22 (±0.99) cm3; w=334; p=0.005), even after adjustment on brain volumes, sex, age, Hamilton De-

pression Rating Scale (HDRS) scores and MDD duration. A ROC analysis showed that a total hippocampal volume threshold of 5.00 cm3 had a 98.2% negative predictive value for acute suicide attempts.
Conclusions: Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts, independently from socio-demographics and MDD characteristics. This difference is related to acute suicide attempts but neither to past suicide attempts nor to duration since the first suicide attempt, suggesting that hippocampal volume could be a suicidal state marker in MDE. Further studies are required to better understand this association.

Keywords: Suicide attempt, major depressive disorder, hippocampal volume, automatic segmentation, MRI
Supported by: Programme Hospitalier de Recherche Clinique AOR10071

171. Effect of a Dietary Supplement on Predisposition to Depressed Mood in Postpartum: 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. Greater severity of postpartum blues (PPB) is associated with onset of PPD, hence, one approach to prevent PPD is to reduce PPB, such as through a dietary supplement. A supplement kit consisting of monoamine precursor amino acids and dietary antioxidants was designed to counter the elevated monoamine oxidase-A levels that occur during PPB. The specific aim of this open-label study was to assess whether this dietary supplement can reduce the intensity of PPB at day-5 postpartum, the typical peak of PPB.
Methods: 26 healthy day-5 postpartum women were recruited into 2 groups: Control group (n=12) not receiving any supplements, Supplemented group (n=14), receiving the dietary supplements (2g tryptophan, 10g tyrosine and blueberry juice+extract). Severity of PPB was quantitated by the change in the visual analogue scale (VAS) from the sad mood induction procedure (MIP).
Results: Univariate analysis of variance demonstrated a significantly greater elevation in depressed mood on the VAS after MIP in controls versus the supplemented group ($F(1,24)= 229.46$, $p<0.001$). A similar effect of group on change in profile of mood symptom scores was also observed ($F(1,24)=25.31$, $p<0.001$).
Conclusions: Administration of the dietary supplement virtually eliminated the intensity of PPB. This supports further investigation of this dietary supplement in a double-blind, randomized, placebo controlled trial, to reduce PPB, as the next phase in developing a dietary strategy to reduce risk of PPD.

Keywords: Postpartum Depression, Dietary Supplement, Monoamine Precursors, Postpartum Blues
Supported by: OMHF, Canada Research Chair

172. Clinical, Biological, and Epidemiological Evidence linking Depression and Dementia

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Background: Depression is associated with dementia. The pathways that link depression to dementia are not well charaterized. This review will address the various models for such pathways.
Methods: A systematic review of epidemiological, clinical, and biological literature on the association between depression and dementia was conducted.
Results: Several models are identified: depression as a risk factor, as a prodrome, as a presenting sydrome, and as a behavrioal syndrome associated with dementia.
Conclusions: The various models linking depression to dementia have different treatment implications and set the stage for different preventative interventions.

Keywords: Depression, Dementia, Prevention

173. Adjunctive Brexpiprazole (OPC-34712) in Patients with Major Depressive Disorder and Sleep Disturbances: An Exploratory Study

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Backgound: Brexpiprazole is a serotonin-dopamine activity modulator (SDAM) that is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors with similar potency, and antagonist at 5-HT_{2A} and noradrenaline alpha$_{1B/2C}$ receptors. The objective of this study was to evaluate the effects of adjunctive treatment with brexpiprazole on sleep disturbance parameters in patients with MDD and inadequate response to antidepressant treatment (ADT) (NCT01942733).
Methods: Patients with MDD and inadequate response to ADT were treated with their current ADT for a period of 2 weeks. Patients who still had an inadequate response, and experienced sleep disturbances, received 8-week open-label treatment with their current ADT and adjunctive brexpiprazole (1 to 3 mg/day).
Results: A total of 44 patients were treated with ADT and adjunctive brexpiprazole. At week 8, improvements from baseline, as measured by polysomnography (PSG; n=40) and the Consensus Sleep Diary for Morning (CSD-M; n=23), respectively, were observed in Sleep Efficiency (10.4% and 13.4%), Total Sleep

Time (49.0 min and 69.9 min), Sleep Onset Latency (19.7 min and 37.1 min), and Wake-Time after Sleep Onset (26.4 and 43.0). The Insomnia Severity Index (ISI) total score was also improved (-9.2, n=41), as well as vigilance, cognition and functioning measured by the Eppworth Sleepiness Scale (ESS) total score (-2.1, n=41) and the Cognitive and Physical Functioning Questionnaire (CPFQ; -8.4, n=44). No new safety concerns were observed compared to previous brexpiprazole studies.
Conclusions: Adjunctive treatment with brexpiprazole may represent a novel strategy for the treatment of sleep disturbances in patients with MDD and inadequate response to ADT.

Keywords: brexpiprazole
Supported by: H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc.

174. Adjunctive Brexpiprazole (OPC-34712) in Patients with Major Depressive Disorder and Irritability: An Exploratory Study

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Background: Brexpiprazole is a serotonin-dopamine activity modulator (SDAM) that is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors with similar potency, and an antagonist at 5-HT_{2A} and noradrenaline $alpha_{1B/2C}$ receptors. The objective was to evaluate adjunctive treatment with brexpiprazole on irritability symptoms in patients with MDD and inadequate response to antidepressant treatment (ADT) (NCT01942785).
Methods: Patients with MDD and inadequate response to ADT were treated with their current ADT for a period of 2 weeks. Patients who still had an inadequate response, and were irritable (IDS-C30 item 6 ≥2), received 6-weeks open-label treatment with their current ADT at the same dose and adjunctive brexpiprazole. Brexpiprazole was discontinued at Week 6, and patients continued with their current ADT up to Week 10. Changes from Baseline at Week 6, and changes between Week 6 and Week 10 were analyzed.
Results: A total of 54 patients were treated with ADT and adjunctive brexpiprazole. At Week 6, improvements from baseline symptoms were observed assessed by Sheehan Irritability Scale (SIS) total score (-21.1, n=50) and SIS Item 1 (-3.5, n=50). More patients stopped having anger attacks during treatment (15 patients), measured by the Anger Attacks Questionnaire (AAQ). Depressive symptoms also improved at Week 6 assessed by MADRS total score (-14.2, n=50). Irritability symptoms re-emerged after brexpiprazole discontinuation assessed at Week 10. Adjunctive brexpiprazole was well tolerated, and no new safety concerns were observed.
Conclusions: Adjunctive treatment with brexpiprazole may represent a novel strategy for the treatment of irritability symptoms in patients with MDD and inadequate response to ADT.

Keywords: Major depressive disorder, Irritability
Supported by: H. Lundbeck A/S

175. Amygdala Volume Is Associated with Helplessness in Adults with Major Depressive Disorder (MDD)

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Background: Helplessness is conceptualized as a product of repeated exposure to uncontrollable aversive events and has been implicated in the etiology of MDD. Functional neuroimaging studies suggest amygdala involvement in negative stimulus processing, as well as a relationship between perceived helplessness and amygdala activation in patients with MDD. However, amygdala morphology has not been examined with regard to self-reported helplessness in depressed individuals. We hypothesized a relationship between amygdala volume and frequency of helpless cognitions, measured by the helplessness factor of the Automatic Thoughts Questionnaire (ATQ), in adults with MDD.
Methods: These preliminary analyses include 34 right-handed adults with MDD (13 male) and 14 healthy control subjects (7 male) ranging in age from 18-45 years who completed structured clinical interviews and the ATQ, and underwent 3T magnetic resonance imaging. Correlation analyses examined ATQ helplessness scores relative to amygdala volumes, determined using FreeSurfer automated software and corrected for intracranial volume, within subject groups and in the combined sample.
Results: Amygdala volumes did not differ between the MDD and healthy control groups ($t(46)=-1.01$, $p=.32$). Adults with MDD had more frequent helpless thoughts ($t(46)=2.40$, $p=.02$) relative to healthy subjects. Helplessness scores were significantly correlated with amygdala volume in the MDD group ($r(31)=.41$, $p=.02$) when controlling for gender. The relationship was not significant in the healthy control group ($r(11)=-.19$, $p=.54$) or in the combined sample ($r(45)=.20$, $p=.19$).
Conclusions: While previous findings have demonstrated associations between functional amygdala activity and helplessness-related cognitions in MDD, our findings suggest that amygdala morphology may also play a role in helplessness.

Keywords: Amygdala, Helplessness, Major Depressive Disorder, Magnetic Resonance Imaging
Supported by: USAMRAA Award# W81XWH-12-1-0109

176. A Randomized, Placebo-controlled Trial of Light Therapy for Bipolar Depression: Antidepressant Efficacy, Side Effects, Changes in Suicidality and Sleep

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Background: Bipolar Disorder (BD) is a major public health concern that is associated with chronic depression, disability and suicide risk. We conducted a 6-week randomized, double-blind placebo-control trial to investigate the efficacy of midday light therapy for bipolar depression. We examined change in depression levels, rates of response and remission.
Methods: We enrolled adults with SCID-confirmed BD-I or II, a current major depressive episode, and stable-dosed antimanic drug therapy. WE excluded patients with psychosis, rapid cycling, OCD, alcohol or substance use disorders, hypomanic or manic symptoms, and recent suicidality. Patients received 7000 lux broad spectrum light therapy OR 50 lux dim red light for 45-60 minutes daily. Weekly, the blinded-clinician rated symptoms with the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement (SIGH-ADS), Mania Rating Scale (MRS), Scale for Suicidal Ideation (SSI) and Systematic Assessment for Treatment Emergent Effects.
Results: From 93 potential participants, we randomized 46 patients to active light vs control comparator. Groups did not differ at baseline; most patients had moderate-severe depression levels. At randomization, the group X vs Y SIGH-ADS depression scores were 30.1±6.1 and 26.1±5.2 (U(1)=5.68, p=0.02, f=0.38), respectively. At Week 6, the group X vs Y depression scores differed significantly: 17.4±9.8 vs 10.4±8.1, respectively (U(1)=6.40 p=0.01, f=0.41). Remission rates (SIGH-ADS≤8) differed significantly between groups; 14.3% (3) of group X vs 56.5% (13) of group Y patients had minimal depressive symptoms by Week 6 ($X^2(1)$ = 8.46, p=0.004).
Conclusions: Original findings provide robust evidence to confirm the efficacy of midday light therapy for major depressive episodes in patients with BD. Added benefits include improved sleep quality and reduced suicidality.

Keywords: Bipolar Disorder, Light Therapy, Clinical Trial, Antidepressant, Novel Intervention
Supported by: National Institute Mental Health (NIMH), K23 MH 082114, Career Development Award, PI – D. Sit

177. Adjunctive Brexpiprazole (OPC-34712) in Patients with Major Depressive Disorder and Anxiety Symptoms: An Exploratory Study

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Background: Anxiety symptoms are common in patients with major depressive disorder (MDD) and are associated with greater severity, impaired functioning, and less favourable outcomes. The objective of this open-label study was to explore the effects of adjunctive brexpiprazole in patients with MDD and anxiety symptoms (NCT02013531).
Methods: Patients with MDD and anxiety symptoms (HAM-A≥20) with an inadequate response to current ADT were enrolled and received open-label ADT+brexpiprazole 1 to 3mg/day (2mg/day target dose) for 6 weeks. Efficacy endpoints included change in clinician-rated MADRS and HAM-A total score from baseline to Week 6, and change in the 92-item patient-rated Kellner Symptom Questionnaire (KSQ, range 0 to 92) total score from baseline to Week 6.
Results: A total of 37 patients were treated with brexpiprazole+ADT, of these 32 patients completed 6 weeks of treatment. Improvements were observed for the LS mean change in MADRS total score from Baseline to Week 6 in patients treated with brexpiprazole+ADT (least square mean change: -19.6) and in HAM-A total score (-17.8). In addition, the mean change from Baseline to Week 6 in KSQ total score (-29.4) also improved. Adjunctive brexpiprazole was well tolerated; the incidence of activating adverse events (akathisia, restlessness, agitation, anxiety, and insomnia) was low (≤5%); and no clinically relevant changes in the mean laboratory test values, vital signs, or ECG parameter values were observed.
Conclusions: Adjunctive treatment with brexpiprazole may represent a novel and effective strategy for treatment of patients with MDD and symptoms of anxiety showing an inadequate response to ADT.

Keywords: Major depressive disorder, Anxiety
Supported by: Lundbeck/Otsuka

178. Computerized Cognitive Behavioral Therapy to Prevent Relapse After Electroconvulsive Therapy: Preliminary Results From a Prospective Pilot Study

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Background: Neuroplasticity is recognized as playing an important mechanistic role in the pathophysiology and potential treatment of psychiatric disease, including Major Depressive Disorder (MDD). Biological treatments that enhance neuroplasticity may provide an opportune time for cognitive and behavioral interventions, allowing for the possibility of synergy among different treatment modalities. Electroconvulsive therapy (ECT) is the most effective treatments for MDD, yet relapse rates following ECT remain unacceptably

high. ECT may induce a state of neuroplasticity wherein learning is enhanced, providing an opportune time for cognitive behavioral therapy (CBT), which may in turn prevent relapse following ECT.
Methods: Patients experiencing a major depressive episode and who achieved response from ECT were recruited to participate in a computerized CBT program. The Montgomery-Asberg Depression Rating (MADRS), Beck Depressive Inventory (BDI), and Quick Inventory of Depressive Symptomatology (QIDS) were used to assess depression severity over a 2-month follow-up period.
Results: Eight patients were enrolled and five completed the 2-month follow-up period. Patients retained gains achieved from ECT treatment over the 2-months follow-up period. All patients had lower BDI and QIDS scores at 2-months follow up (mean BDI 12.0, SD 12.3; mean QIDS 9.4, SD 9.7) compared to their scores immediately after index course of ECT (mean BDI 24.6, SD 15.7; mean QIDS 16.4, SD 8.0). Mean MADRS scores at 2-months follow-up (mean 14.2, SD 12.0) were slightly lower compared to baseline (mean 14.6, SD 7.1).
Conclusions: This study provides preliminary evidence that computerized CBT following ECT is feasible and may prevent relapse in depressed patients.

Keywords: Major depressive disorder, Electroconvulsive therapy, Cognitive behavioral therapy, Neuroplasticity
Supported by: NIMH; American Psychiatric Foundation/Janssen

179. Inattention and Disrupted Resting State Functional Connectivity of the Cerebellar Default Node in ADHD

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Background: Abnormal spontaneous interactions between the brain's default mode network (DMN) and networks associated with attention to the external environment (sensory, salience and dorsal/ventral attention networks) have been hypothesized to underlie attentional deficits in ADHD. These networks include cerebellar components that are accessible stimulation targets for therapeutic neuromodulation. We thus tested whether spontaneous functional connectivity (FC) of the cerebellar node of the DMN (CerDMN) is disrupted in ADHD and whether this FC relates to individual differences in inattention.
Methods: 23 adults with ADHD and 23 age-, IQ-, and sex-matched healthy controls underwent resting state fMRI (10 minutes) and completed the Adult ADHD Self-Report Scale (ASRS). The mean time series of seed regions in the CerDMN were extracted, and FC with the whole brain was calculated. Within- and between-group differences in FC were assessed. Additionally, relationships between the ASRS inattention subscale and individual differences in FC were assessed for between-group interactions. All analyses were conducted at the whole brain, voxel-wise corrected level (FLAME; $Z > 2.3$, cluster-based $p < 0.05$).
Results: Within both groups, CerDMN was functionally connected with cortical DMN regions. FC of the CerDMN in ADHD compared to healthy controls showed less anti-correlation with widespread regions of salience and dorsal/ventral attention networks. Inattention positively correlated with FC between CerDMN and regions within the dorsal attention network in healthy controls but not in ADHD.
Conclusions: This work provides novel evidence of impaired CerDMN decoupling with cortical networks in ADHD and highlights a role of the cerebro-cerebellar interactions in cognitive function.

Keywords: cerebellum, adhd, default mode network, attention, inattention
Supported by: NIH

180. Neurocognitive Correlates of Shyness and Sociability in Children

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Background: Shyness and sociability are two independent personality dimensions, each of which corresponds with distinct behavioral and psychophysiological correlates that are conserved across development, culture, and phylogeny (Asendorpf, 1991; Cheek & Buss, 1981; Schmidt & Buss, 2010). Yet, relatively little is known regarding how shyness and sociability are instantiated and maintained in the brain, particularly in terms of brain function during the processing of non-social stimuli and during childhood.
Methods: Using a 3-stimulus auditory oddball task, we examined whether variation in shyness and sociability were related to the P3 ERP brain response to processing task-relevant, novel, and standard auditory tones in 53 typically developing 10-year-old children. ERP amplitudes were measured at four midline scalp sites (Fz, FCz, Cz, Pz).
Results: We found significant positive correlations between shyness, but not sociability, and target P3 amplitudes across all four head sites, r's = .24 to .3, p's < .05. A Fisher's r-to-z test of correlation coefficients between the target P3 amplitude at Pz and (a) shyness, and (b) sociability were different, $z = 1.7$, $p < .05$, indicating the target P3 response was a specific predictor of shyness, with no overlaps in sociability.
Conclusions: These findings suggest increased vigilance, implicating increased attentional and working memory operations, in the processing of non-social task-relevant stimuli in the auditory domain among children who are shy. These findings extend recent work by our group demonstrating distinct neurocognitive correlates of increased vigilance to social stimuli in early visual processing among adults who are shy (Jetha et al., 2012).

Keywords: Shyness, Sociability, ERP, P300, Auditory oddball
Supported by: SSHRC; NSERC

181. TMS for Executive Function Deficits in Youth with Autism Spectrum Disorder

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Background: There are no satisfactory treatments for executive functioning(EF) deficits that predict real-world disability in high functioning autism spectrum disorder(HF-ASD). Our randomized, double-blind, sham-controlled pilot study suggests that four weeks of repetitive transcranial magnetic stimulation(rTMS) to dorsolateral prefrontal cortex(DLPFC) can significantly improve EF performance in schizophrenia (Cohen's d=0.91). As there may be overlapping etiology resulting in EF impairments in HF-ASD and schizophrenia, the same biological treatments may improve deficits in both conditions. Objective: To complete a pilot study exploring the novel application of rTMS to DLPFC for EF deficits in HF-ASD. Our primary aims are to:(i)determine if our rTMS protocol can be successfully applied in HF-ASD, (ii)examine whether active rTMS improves EF performance, (iii)use neuroimaging in a pre/post design to identify mechanisms of treatment response.
Methods: We are using a randomized, double-blind, sham-controlled design comparing active(20Hz) vs. sham rTMS applied 5 days/week for 4 weeks bilaterally to DLPFC in young people with HF-ASD(N=40,16-25years). EF performance measures and structural/functional neuroimaging measures (MRI/DTI/rs-fMRI and task-based fMRI) are being evaluated before and after the 4-week intervention.
Results: We have now started recruitment and have four subjects who have entered into our study protocol within a short period of time. Initial participants are tolerating our protocol well. Over the next six months, we anticipate that twelve HF-ASD participants will have completed our protocol.
Conclusions: At SOBP 2015, we will present our novel protocol, preliminary feasibility data, and associations between baseline cognitive performance and DLPFC structure, activation and white matter microstructure linking DLPFC

Keywords: Autism Spectrum Disorder, Executive Functioning, Repetitive Transcranial Magnetic Stimulation, Brain Imaging, Clinical Trial
Supported by: Ontario Mental Health Foundation, AACAP Pilot Research Award, U of T Dean's Fund, CAMH AFP Innovation Fund

182. Associations of Fractional Anisotropy and Neuropsychological Dysfunction in AD/HD and non-AD/HD Youth

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Background: Inconsistency of results across diffusion tensor imaging (DTI) studies that compare Attention-Deficit/Hyperactivity Disorder (AD/HD) to non-AD/HD controls complicates our understanding of the role of white matter abnormality in AD/HD. Rather than simply compare groups, this study took an alternative approach that examined whether the relationships between various cognitive abilities and fractional anisotropy (FA) differed between AD/HD and non-AD/HD.
Methods: DTI data from 69 Combined-subtype AD/HD and 72 healthy adolescents were examined using tract-based spatial statistics (TBSS). Neuropsychological test data assessing attention, response inhibition, and reward domains were reduced using PCA into 4 factors. FSL GLM analyses identified group differences in the slopes of the associations of each factor with all white matter FA voxels.
Results: Significant TFCE-corrected group differences were found in the relationship between a factor that represented lapses of attention and inadequate reflection before responding and numerous tracts, including brainstem, both internal/external capsules, other corticospinal tracts, bilateral longitudinal and uncinate fasciculi, and corpus callosum genu/forceps minor. Because AD/HD participants were impaired on tests loading onto this cognitive factor, AD/HD's shallower linear slope indicated impairment occurred with less organized AD/HD brain-behavior associations. No group differences were found in the relationship of FA with other reward or response inhibition performance-related PCA-derived factors.
Conclusions: This study linked a specific type of cognitive dysfunction to the variability of AD/HD white matter organization in widespread white matter tracts, including several frequently reported to be abnormal in AD/HD. It provides a novel framework for examining contributions of white matter abnormalities to AD/HD-related impairments.

Keywords: Fractional Anisotropy, AD/HD, Cognitive Dysfunction, White Matter, Diffusion Tensor Imaging
Supported by: R01 MH080956

183. Neural Mechanisms of Uncertainty Processing in Children with Autism Spectrum Disorders

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Background: Autism spectrum disorder (ASD) is characterized by insistence on sameness and an aversion to unpredictability; however the neural mechanisms of uncertainty processing in ASD are not well understood.

Methods: Twenty-six youth with ASD and 21 matched controls 9-18 years old participated. During fMRI scanning, participants completed a task that presented a cue that indicated whether there was a 50% or 100% chance of seeing either a social or nonsocial images.
Results: While processing cues for uncertain social images, the ASD group demonstrated reduced activation in the right caudate nucleus and left inferior frontal gyrus, whereas while processing the uncertain social images themselves, the ASD group demonstrated greater activation in the right middle frontal gyrus and left superior frontal gyrus. While processing cues for uncertain nonsocial images, the ASD group demonstrated reduced activation in the left ventral and dorsal striatum, bilateral frontal pole, left middle frontal gyrus, left paracingulate gyrus, and right precentral gyrus; whereas while processing the nonsocial images themselves, the ASD group showed reduced activation in the right OFC and right thalamus. Activation in the right caudate nucleus during the presentation of uncertain images predicted scores on the Intolerance of Uncertainty Scale in the ASD group, p = .018.
Conclusions: Attenuated activation in multiple frontostriatal regions linked with salience and reward processing during the presentation of cues predicting uncertain social and nonsocial outcomes suggests a neural mechanism for insistence on sameness that may inform the development of interventions that more effectively address insistence on sameness symptoms in ASD.

Keywords: Autism spectrum disorder, insistence on sameness, uncertainty, functional MRI
Supported by: R01MH073402; U54HD079124

184. Peripheral Blood Markers of Homocysteine, Paraoxonase1 (PON1) Activity and Oxidative Stress in Autism

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Background: Autism is a behaviorally defined disorder of unknown etiology that is thought to be influenced by genetic and environmental factors. High levels of homocysteine and oxidative stress are generally associated with neuropsychiatric disorders. Oxidative damage may play a central role in this pathogenesis, together with the interconnected transmethylation cycle and transsulfuration pathway.
Methods: The purpose of this study was to compare the level of oxidative stress and other biomarkers in children with autism to corresponding values in age-matched healthy children. We measured ceruloplasmin, transferring, total homocysteine (tHcy), vitamin B12, paraoxonase and arylesterase activities of human paraoxonase 1 (PON1) in plasma and glutathione peroxidase (GPx) activity in erythrocytes from 44 children: 22 with autism (age: 7.23±1.83 years) and 22 controls (age: 7.83±1.71 years). The diagnosis of autism was made by a child neuropsychiatrist using criteria for DSM-IV-TR.
Results: We found statistically significant differences in tHcy levels and in arylesterase activity of PON1 in children with autism: 8.74±2.17 μmol/L ($p \leq 0.01$) and 82.13±7.09 kU/L ($p \leq 0.005$) when compared to the control group, and found that there was a strong negative correlation between tHcy and GPx activity and the vitamin B12 level was low. Levels of major antioxidant proteins namely, transferrin (0.26 ± 0.02) mg/ml and ceruloplasmin (2.28 ± 0.24) mg/ml in the serum, were significantly reduced in autistic children and also it shows positive pearson correlation ($r=0.054$, $n = 36$, $p \leq 0.0005$).
Conclusions: In conclusion, existing evidence suggests a role for glutathione metabolism, the transmethylation cycle, and the transsulfuration pathway in relation to the protective PON1 enzyme activity. Although these findings should interpret with caution, and larger, more standardized studies are warranted.

Keywords: Autism, antioxidant protein, homocysteine, human paraoxonase, glutathione peroxidase

185. Predicting Functional Activation of Reading Subnetworks with a Novel Reading Tendency Index

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Background: Reading Disability (RD) is prevalent in children with ADHD. Proficiency in reading fluency requires good decoding skills and ability to recognize words, which may be affected by ADHD impairments. We introduce a novel index that quantifies imbalances between reading strategies [e.g., sight reading vs. decoding] and hypothesize that this index will predict functional activation of specific reading subnetworks during an fMRI reading task.
Methods: 41 boys (14 control, 15 ADHD, 11 ADHD/+RD) completed two fMRI paradigms, weighted toward decoding or word recognition. Drift rates for each skill were calculated using the Drift Diffusion Model. The difference between the inverse drift rates generated the novel Reading Tendency Index, which classified three reading groups (Decoders, Fluent/Balanced, and Sight Readers). Functional activation patterns during a word recognition fMRI task were evaluated between groups.
Results: Contrasts based on diagnostic criteria (i.e., ADHD and ADHD/+RD) did not reveal significant functional activation differences related to reading subnetworks. However, when grouping based on the novel index, Decoders evidenced hyperactivation of the left iPL (BA 39/40) and IFG (BA 44) relative to Fluent/Balanced readers and hypoactivation of left middle temporal gyrus (BA 22) compared to either group.
Conclusions: The novel Reading Tendency Index effectively delineated subjects such that clusters of impairments and functional activation differences in reading subnetworks corresponded with theoretical predictions. While larger studies are needed to validate the index, the current study demonstrates a powerful classification of readers based on individual tendencies, rather than disabilities, which has implications for remediation.

Keywords: ADHD, Reading, fMRI, lexical decision, cognitive flexibility
Supported by: NIH 5R01 MH065420-06S (PI: JAS); Young Investigator Award; PI: BMM (Dept. Psychiatry and Behavioral Neurosciences at WSU); Lycaki-Young Funds (State of Michigan)

186. Neurocognitive Similarities and Differences Between Obsessive-Compulsive and Related Disorders

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Background: Patients with Obsessive-Compulsive and Related Disorders (OCRDs) are impaired in a broad range of cognitive tasks. Accumulating evidence suggests neurocognitive mechanisms mediating compulsivity (attentional set-shifting, reversal learning, habit, executive planning) and impulsivity (motor inhibition, delay aversion, decision-making), subserved by neural activity within specific cortico-striatal loops, variably contribute toward compulsive activity in OCRDs, and may extend to disorders of addiction. Better understanding of the neuropsychological basis for these deficits may guide nosological classification, treatment-allocation and treatment-development.
Methods: Using a similar neurocognitive battery, subjects with body dysmorphic disorder (BDD) (n=12), obsessive compulsive personality disorder (OCPD) (n=21) and OCD with (n=10) and without alcohol use disorder (AUD)(n=15) were compared with healthy controls (n=16; n=15; n=24) in a series of three studies.
Results: Subjects with OCD, BDD and OCPD manifested impaired cognitive inflexibility on the extra-dimensional set-shift task (respectively p=.01; p=.001; p=.03) suggesting a common mechanism. Whereas BDD showed increased motor impulsivity (stop-signal reaction time p= .04) and delay-aversion (p=.03) on the Cambridge Gamble Task (CGT), OCD+AUD showed poor quality of decision-making on the CGT (p<.05). In contrast, OCPD showed increased thinking time on the Stocking of Cambridge executive planning task (p<.001).
Conclusions: These results are consistent with the recent classification of BDD with OCD and suggest additional areas of decision-making impulsivity that contribute to the psychopathology of BDD and addiction. In OCPD, the neurocognitive changes show ecological convergence with traits such as perfectionism, rigidity and slowness and also overlap with those of OCD, consistent with re-classification of OCPD within the OCRDs.

Keywords: obsessive, compulsive, neurocognitive, mechanisms, nosology
Supported by: European Union

187. The Use of Transcranial Alternating Current Stimulation to Decrease Cognitive Impulsivity

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Background: Cognitive impulsivity is the process of acting prematurely without foresight and plays an important role in decision-making. There is evidence that theta band oscillations of the prefrontal cortex are associated with the inhibitory control of cognitive impulsivity. The goal of this work was to measure whether cognitive impulsivity as assessed by the delay-discounting task can be influenced by transcranial alternating current *stimulation (*tACS), which allows non-invasive modulation of brain oscillations.
Methods: We conducted a randomized, double-blind, sham-controlled study with fourteen adults who received two 30-min stimulation sessions (active, sham) separated by 7 days. We assess potential side-effects at each session. Active tACS targeted the prefrontal cortices at 6Hz. Sham consisted of the same electrode montage but with no active stimulation. The delay-discounting task was administered immediately before and after each stimulation session. Participants had to choose between immediate but smaller rewards and delayed but greater rewards in 144 trials. Discounting k-values were calculated and entered into Wilcoxon Tests.
Results: Active tACS decreased discounting compared to sham tACS ($z=-2.040$, $p<0.005$): participants favoured large and delayed rewards instead of small and immediate rewards when they received active than sham tACS. The most common side effect reported by the participants was tiredness. Integrity of blindness was observed from both participants and the investigator administering the delay-discounting task.
Conclusions: Our findings suggest that tACS can modulate cognitive impulsivity. This approach may suppress cognitive impulsivity in neuropsychiatric populations such as substance use disorders, but more studies are needed to assess the clinical relevance and transferability of these results.

Keywords: cognitive impulsivity, transcranial alternating current stimulation, delay-discounting, decision-making

188. Neural Correlates of Choice Strategies Contributing to Poor Causal Awareness in Bipolar Disorder

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Background: Optimal decision-making requires planning and working memory processes in order to integrate new learning about action values, and to form causal awareness. Unfortunately,

deficits in these capacities are widely reported in bipolar disorder (BD). Further, impulsivity, a trait feature of BD, may favor behaviors that afford immediate reward, at the expense of longer term goals. As such, we predicted that individuals with BD would predominantly use a simpler heuristic strategy (e.g. win-stay-lose-shift, WSLS) as opposed to a more computationally-expensive (e.g. model-based RL) method on a probabilistic choice task.
Methods: 19 euthymic individuals with BD and 23 matched controls performed a two-choice probabilistic reward-learning task during functional MRI. We examined choice behavior using a WSLS analysis and the neural regions modulating different choice strategies
Results: Despite expectations, BD did not follow a WSLS strategy more than controls, but tended to vacillate erratically between choices. Within BD, activity in regions including the postcentral gyrus, inferior parietal lobe (IPL), and dorsolateral prefrontal cortex (dlPFC) was attenuated during exploitative actions in those with poorer causal awareness. Impulsivity, but not working memory, was positively correlated with proportion of switches and negatively correlated with causal awareness in the BD cohort.
Conclusions: Evidence for a predominant choice strategy in BD was inconclusive. Lack of inhibitory control however may lead to increased switching in some individuals with BD, causing inefficient tracking of action values, and resulting in diminished causal awareness. Given the large variance in choice vacillation, this result may more broadly reflect impulsivity rather than a disorder-specific mechanism.

Keywords: bipolar disorder, causal awareness, win-stay loss-shift, impulsivity, fMRI
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189. The Effects of Cannabis Use on Emotion Processing in Depressed and Non-depressed Populations. An Event Related Potential Study

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Background: The effects of Cannabis use on mood states, specifically emotion processing are unclear. Cannabis consumption has been related to self-medication for mood disorders such as depression, a growing trend in adolescent populations. The efficacy of this approach, both within a recreational or medical application is controversial, with negative and positive possible outcomes from cannabis exposure.
Methods: Participants were scored as depressed using a cutoff of 16 on the CESD (Radloff,1977). A control group was compared to a self-reported cannabis users group. A total of 9 participants from 39 non users constituted a depressed sub-group, 11 from 27 a depressed sub-group of users. An Event related Potential Paradigm was then used to evaluate their ability to process female and male emotional facial expressions both explicitly and implicitly, as well as empathetically.
Results: Cannabis users overall had decreased P1 and P3 compared to controls, with depressed users presenting the largest reduction in amplitude. Non-depressed controls presented increased P3 amplitude during empathic processing compared to the other tasks and to all users and depressed controls ($F(6,372)=2.46$; $p<.05$). In all users but not depressed controls this was accompanied by reduced P1 amplitude during empathetic processing most prevalent for angry faces ($F(6,372)=2.76$; $p<.05$).
Conclusions: Cannabis use appears to modulate the processing of emotion in the brain. There are significant differences in the ERP's of cannabis users compared to non-users for emotional stimuli. These effects are more marked in individual's who are emotionally compromised. Further investigation is needed to clarify why these differences exist.

Keywords: Cannabis, Depression, Event Related Potential, Emotion, Mood disorder

190. Cognitive Impairment in Patients with Inadequate Response to Antidepressants

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Background: Cognitive impairment in patients with major depression has been reported previously, however the interpretation of findings is often hindered by small sample sizes. To address this gap, we evaluated the deficits in cognitive functions both cross-sectionally and longitudinally in two large treatment studies of patients with an inadequate response to up to three antidepressant trials.
Methods: Cognitive function was assessed at baseline and end of treatment in patients with MDD and inadequate response to antidepressants who participated in one of two phase 2 randomized, placebo-controlled trials. Both studies involved six week treatment with novel, putative antidepressant agents as adjunct to ongoing treatment with antidepressants (study 1; N=322; study 2; N=346). A separate study was also conducted in healthy volunteers (N=240) matched for sex, age and educational level. Cognition was assessed using the CANTAB battery that included tests of memory, attention and executive function. A composite cognitive performance score was calculated based on a factor analysis.
Results: At baseline patients in both depression studies showed significant deficits in overall cognitive performance and all cognitive functions assessed compared to healthy volunteers. In placebo-treated patients (study 1: N=97; study 2: N=90) overall performance deficits continued to the end of treatment despite substantial depression remission rates in both studies (study 1= 31%; study 2= 29%). Persistent impairments were also observed for individual domains (working memory, executive function and attention).
Conclusions: Patients with inadequate response to antidepressants show clinically significant cognitive deficits that persist despite improvement of their depression. These deficits may contribute to persistent functional deficits.

Keywords: Major Depression, Cognitive Impairment, Treatment-resistant depression

191. Decision-Making Deficit and its Medial Prefrontal Implications among First Degree Relatives of Suicide Completers

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Background: Suicide has been shown to be heritable. In the present study, we aimed at investigating neurocognitive endophenotypes in relatives of suicide completers using neuroimaging. We particularly focus on the neural activity pertaining to risky and safe decision making process, because its impairment has been previously implicated in suicide attempters in comparison to patients and healthy controls.
Methods: Seventeen healthy relatives of suicide completers who suffered from major depressive disorder (RSC), 18 healthy relatives of patients with a history of depression without any personal or family history of suicidal acts (RPC) and 19 healthy relatives of healthy controls (RHC) were recruited. We acquired both structural and functional magnetic resonance imaging scans while participants underwent Iowa gambling task (IGT). Group differences in blood-oxygen-level dependent responses were analyzed with SPM12.
Results: In addition to poor decision making in Iowa Gambling task in RSC relative to RHC, RSC also exhibited reduced BOLD activities differences than RHC in cluster predominantly the medial frontal gyrus (BA10/32, Z = 3.90, peak voxel: 2, 50, 6) between risky and safe decision making process in IGT. No significant group differences were observed when either groups comparing with RPC.
Conclusions: Relatives of suicide completers present particular decision making deficit potentially related to medial prefrontal cortex during risky decision making process that reflect either heritable traits of vulnerability or potential protective factor. Future combined study with suicide attempters is necessary to clarify the contribution of this region to the heritability of suicidal vulnerability.

Keywords: suicide, endophenotype, vulnerability, depression, fMRI
Supported by: AFSP

192. Impulsivity in Bipolar Disorder Types I, II and Major Depressive Disorder

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Background: Increased impulsivity has been associated with mood disorders, in particular bipolar disorder (BP) when compared to controls. Few studies, however, have compared impulsivity between major depressive disorder (MDD) and BP. Furthermore, there has been little research pertaining to the differentiation between levels of impulsivity in BP subtypes, including bipolar type I (BPI) and bipolar type II (BPII).
Methods: Participants were recruited from the Mood Disorders Program of the McGill University Health Center in Montreal, Quebec. Data was gathered using structured diagnostic interviews (SCID), family history of psychiatric illness questionnaire and medical chart review. Impulsivity scores were gathered using the Barratt Impulsiveness Scale (BIS); a self-reported questionnaire measuring the attentional, motor, and nonplanning subscales of impulsivity. Linear regressions were conducted to examine the association between type of mood disorder diagnosis and impulsivity in mood disorder subjects.
Results: Subjects with BP (I andII), when compared to subjects with MDD scored higher on the BIS total (Unst. B = 5.073, p = .014) as well as on the motor (Unst. B = 2.043, p = .012) and non-planning (Unst. B = 1.998, p = .020) subscales. When the BP subjects were divided into BPI and II groups, the BPII group scored higher on the BIS total (Unst. B = 10.361, p = .000), as well on the attentional (Unst. B = 2.364, p = .004), motor (Unst. B = 2.986, p = .004), and nonplanning (Unst. B = 4.050, p = .000) subscales when compared to MDD group. BPII subjects also scored higher on the BIS total (Unst. B = 5.945, p = .033), as well on the attentional (Unst. B = 2.136, p = .035), and nonplanning (Unst. B = 2.485, p = .027) subscales when compared to BPI subjects. BPI subjects' scores were not significantly different on either the BIS total or its subscales when compared to MDD subjects.
Conclusions: In accordance with previous research, the BP group reported significantly higher levels of total, motor and nonplanning impulsivity than the MDD group. More specifically BPII subjects scored significantly higher on all scales of impulsivity than the MDD subjects. Of interest, BPII subjects, when compared to BPI subjects, reported significantly higher levels of total, attentional and nonplanning impulsivity but not motor impulsivity. These findings suggest that impulsivity traits in BPII are distinct when compared to other mood disorder subtypes.

Keywords: Mood, impulsivity, depression, bipolar

193. Reward Delivery Enhances Encoding of Upcoming Information: A Novel Paradigm for Detecting Memory Deficits in Anhedonic Depression

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Background: Major Depressive Disorder is characterized by poor memory for positive material. We hypothesize that this is due to anhedonia at encoding: in healthy adults, brain reward networks boost responding in memory systems and enhance consolidation, but these interactions are weakened in anhedonic depression. This work aimed to establish that reward delivery improves memory in a community sample, in anticipation of future tests in depression.
Methods: We developed an encoding paradigm in which participants view 240 natural and man-made images and decide to keep or reject each one. Decisions are reinforced by delivery of "rewards" (monetary feedback) or "zeros" (no monetary feedback), and the reinforcement rate varies throughout the task. Participants return a day later for a surprise recognition memory test. The paradigm was tested twice (Experiment 1: n = 38, behavioral; Experiment 2: n = 22, functional magnetic resonance imaging [fMRI]).
Results: Memory was better for images that followed rewards versus zeros in both experiments (Zs > 4.03, ps < 0.001). A "reward-zero" fMRI contrast in Experiment 2 revealed strong responses in bilateral hippocampus (left, Z = 4.58; right, Z = 5.17) and ventromedial prefrontal cortex (Z = 4.94), regions implicated in episodic encoding and reward valuation, respectively (p < 0.05, FWE-corrected).

Conclusions: This new paradigm reveals robust effects of reward delivery on recognition memory, along with strong activation of brain regions associated with reward valuation and episodic encoding. We are currently using this paradigm to test our prediction that reward delivery will not enhance memory in depressed adults.

Keywords: Memory, Reward, Anhedonia, Depression, fMRI
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194. Amygdala Response to Selective Emotion Processing Conditions at Baseline Predicts Antidepressant Treatment Response to Scopolamine in Major Depressive Disorder

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Background: Predicting antidepressant response will help optimize treatment for Major Depression(MDD). The muscarinic antagonist scopolamine produces rapid antidepressant effects and modulates attention in a stimulus dependent manner in healthy subjects(HC). We hypothesized that the pretreatment response to emotional stimuli in the amygdala, a structure implicated in MDD pathology, predicts antidepressant response to scopolamine.
Methods: 15 HC and 14 un-medicated MDD patients performed a selective attention task during fMRI before and after treatment. Superimposed pictures of faces/houses were matched for identity of faces(AF) or houses(AH). The faces expressed happiness(AFh, AHh) or sadness(AFs, AFs). Response requirements were independent from emotion. BOLD signal was averaged across voxels for each subject/task condition in anatomically defined amygdala. Pre-treatment BOLD signal was correlated with the %change in depressive symptoms after scopolamine. Conditions with significant results were compared between treatment responders, non-responders, and HC at baseline, and responders and non-responders post-scopolamine.
Results: BOLD signal in the amygdala during AFs correlated with the treatment outcome in the left(r=-.59,p=0.03) and bilateral amygdala(r=-.56 p=0.04). The baseline BOLD signal response to AFs in HC differed from pretreatment BOLD response in subsequent treatment responders(N=6)(p0.05).
Conclusions: The magnitude of pretreatment BOLD response in the amygdala during AFs correlated with treatment response to scopolamine. Thus, pre-treatment activity in the amygdala during selective emotion processing conditions may constitute a biomarker of antidepressant response. The post-scopolamine shift in BOLD response in scopolamine responders suggests a change in stimulus-dependent neural response, likely driven by attenuation of cholinergic activity in the amygdala.

Keywords: major depression, amygdala, fMRI, scopolamine, emotional processing
Supported by: NIMH IRP

195. The Effect of an Acute Bout of Aerobic Exercise on Sustained Attention and Motor Inhibition Among Adolescents With and Without Bipolar Disorder

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Background: Medial frontal dysfunction during attention & executive control tasks is reported in adolescents with bipolar disorder (BD). Aerobic exercise in healthy participants (HC) can improve neurocognitive function, and exercise benefits in those with BD have been widely discussed. This study combines this research to examine exercise effects in adolescents with and without BD using BOLD fMRI of the *sustained attention to response task* (SART) before and 30 minutes following aerobic exercise.
Methods: Participants: fifty 13-19 year-olds (*M*=16.5, *SD*=1.6, 42% male, 30 BD adolescents – active mania excluded; 20 HCs). SART: button presses during rapid serial presentation of numbers 1-9, but inhibition for the number 3; practice controlled for session effects. Exercise: 20 minutes at 60 revolutions per minute on stationary bicycle-ergometer maintaining 60-80% of age-estimated maximum heartrate. Analysis: ANOVAs for behavioral and BOLD fMRI data.
Results: Post-commission-error RT decreased after exercise across groups. Planned comparisons found higher activation in rostral ACC, dorsal ACC and PCC for adolescents with BD>HC pre-exercise and BDpre>BD post-exercise, but no difference BD-post>HCpre. Event analysis of commission-errors produced the same pattern in PCC.
Conclusions: Exercise mitigated over-reactivity to error in behaviour. Findings of medial frontal cortex dysfunction in BD adolescents were replicated. Novel findings revealed reductions in cingulate activation for adolescents with BD post-exercise that approximated HC baseline. These results provide a scientific basis for brain related changes in behaviors realized after a single session of exercise. Future investigations will examine longitudinal cascading effects of regular exercise on everyday symptoms in adolescents with BD.

Keywords: bipolar disorder, adolescents, attention and inhibition, exercise intervention, BOLD fMRI
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196. Distinguishable Patterns of Inter-regional Connectivity Within a Win/loss Anticipation Network in Depressed Individuals With Bipolar Disorder, Depressed Individuals With Major Depressive Disorder, and Healthy Controls

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Background: Bipolar disorder (BD) is often misdiagnosed as major depressive disorder (MDD), especially during depressive episodes,

which leads to inadequate treatment. Neuroimaging studies directly comparing depressed individuals with BD (BDd) and depressed individuals with MDD(MDDd) may help provide biomarkers to distinguish BDd from MDDd. We previously demonstrated abnormally elevated activity in fronto-striatal reward circuitry during win anticipation in BDd. We aimed to compare inter-regional functional connectivity during win/loss anticipation in BDd, MDDd and healthy controls (HC).

Methods: BDd(n=31), MDDd(n=39), and HC(n=36) were scanned during a reward task. A network of 18 regions (e.g.,right medial frontal pole [RFPmed], anterior cingulate gyrus [ACC], right and left frontal pole [RFP,LFP], ventral striatum [RVS,LVS], occipital pole [ROP,LOP], occipital fusiform gyrus [LOFFg,ROFFg], and lateral inferior occipital cortex [LLOCinf,RLOOCinf]) involved in win/loss anticipation was identified across all participants using FSL5.0. Graph modeling using IMaGES algorithm (TETRAD-5.1.0-6) identified connections among those regions.

Results: IMaGES revealed that BDd and MDDd had similar fronto-striatal connectivity patterns during loss anticipation (RFP-RFPmed,ACC-RVS-LVS) that were less dense than the connectivity pattern observed in HC (RFP-LFP-RFPmed-ACC-RVS-LVS). During win anticipation, BDd had denser connectivity among fronto-striatal regions (LFP-RFP-RFPmed-ACC-RVS-LVS) than MDD (LFP-RFP-RFPmed and ACC-RVS-LVS subnetworks were disconnected) and HC (LFP-RFP, ACC-RVS-LVS). Connectivity among occipital regions was, however, the most dense in MDDd (LOP-ROP-ROFFg-LOFFg,ROP-LLOCinf), with fewer connections in HC (LOP-ROP- LLOCinf,LOFFg-ROFFg) and BDd (ROP-LLOCinf,LOFFg-ROFFg).

Conclusions: Altered fronto-striatal and occipital connectivity patterns during win anticipation distinguished BDd from MDDd and HC, and might reflect a neurobiological mechanism underlying abnormally increased attention to potentially rewarding stimuli in BDd.

Keywords: Bipolar disorder, Major depressive disorder, fMRI, reward, graph modeling

Supported by: This study was supported by National Institute of Mental Health (NIMH) grant R01 MH076971 to Dr. Phillips

197. Neurocognitive Predictors of Response in Treatment Resistant Depression (TRD) with Deep Brain Stimulation (DBS) Therapy

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Background: Deep Brain Stimulation (DBS) is a neurosurgical intervention with demonstrated effectiveness for Treatment Resistant Depression (TRD), but longitudinal studies on the stability of cognitive parameters following treatment are limited. The objectives of this study are (i) identify baseline cognitive predictors of treatment response to SCG DBS for unipolar TRD and (ii) examine neurocognitive performance, pre-surgery and after 12 months of Subcallosal Cingulate Gyrus (SCG) DBS stimulation.

Methods: Twenty unipolar TRD patients received SCG DBS over a 12 month period. A standardized neuropsychological battery was used to assess a range of neurocognitive abilities at baseline and was repeated after 12 months. Severity of depression over this time was evaluated using the 17 item Hamilton Rating Scale for Depression (HRSD-17).

Results: The Finger Tap Test, a measure of psychomotor processing speed predicted treatment response and was independent of improvement in mood. Change in verbal fluency was the only neuropsychological test that correlated with change in mood. There was no deterioration in cognitive function at the follow up period relative to baseline.

Conclusions: This was an open label study with a small sample size which is a limitation of the study. Practice effects of the neuropsychological testing could explain the improvement from baseline to follow up on some tasks.Psychomotor speed may be a useful baseline predictor of response to SCG DBS treatment. SCG DBS had no deleterious effects on cognition over the 12 month follow up period.

Keywords: Deep Brain Stimulation, Neurocognition, Treatment Resistant Depression, Prediction of Response, Therapy

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198. Hypoactivation of Key Emotion Processing Regions during Facial Affect Perception in Chronic Pain Patients

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Background: Depression and chronic pain are often comorbid, with common neural underpinnings. Understanding how patients with chronic pain process emotional content may elucidate common neurobiological- phenomenological substrates. This study aims to identify cerebral mechanisms of emotion regulation using a facial emotion processing paradigm among patients with chronic pain.
Methods: Twenty-six non-depressed patients with chronic non-neuropathic back pain and 26 healthy comparisons (HC) underwent fMRI while performing a facial emotion matching task. Group analyses were conducted for face emotion versus shape matching using SPM8 ($p<.05$, corrected). Activation was extracted from regions with significant group effects and correlated with affective and pain questionnaires in the chronic pain group.
Results: Patients demonstrated hypoactivation during facial emotion presentations, relative to HC, in regions relevant to emotion processing, including right prefrontal cortex, right cingulate cortex, left superior temporal gyrus, and ventral basal ganglia, bilaterally ($ps < .003$; Figure 1). Pain intensity scores were positively correlated with cingulate cortex activity, and fatigue scores were negatively correlated with basal ganglia activation in the pain group ($ps<.05$).
Conclusions: Chronic pain patients show hypoactivation in key areas related to emotion; the opposite effect of what has generally been found among depressed patients. Hypoactivation in the basal ganglia is associated with fatigue, while prefrontal cortex activity was related to pain intensity ratings. Chronic pain is associated with distinct alterations in emotion processing, which may be relevant to the comorbidity between these conditions.

Keywords: Chron pain, Emotion perception, fMRI, Amygdala
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199. Impaired Recognition of Subliminal Happy Faces in Remitted Mood Disorders

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Background: Major Depressive Disorder and Bipolar Disorder (hereafter any mood disorder, AMD) are associated with negatively biased emotional processing. Some, but not all, studies suggest that depressed individuals selectively attend to sad faces compared to angry or happy faces. Attentional bias toward sad faces and away from happy faces may be present in remitted/euthymic AMD (rAMD). The present study predicted increased detection of sad faces and decreased detection of happy faces in rAMD relative to healthy controls (HC), in a subliminal emotional face processing task.
Methods: Twenty-two rAMD participants (mean age=22.45, 17 female) and five HCs (mean age=24.00, 3 female) completed an emotional face processing task. In the task, participants viewed subliminally presented (33ms) happy faces, sad faces, a new face identity, or oval shapes at jittered intervals masked by a neutral face, and were asked to identify any changes in the face stimulus. Signal detection index (d') for subliminal stimuli was the dependent variable.
Results: MANOVA and comparison of means revealed that rAMD participants demonstrated lower d' for happy faces relative to HCs, $p<.03$, with no group differences in detection of sad faces, new faces, or ovals. Reaction time did not differ between groups for any stimuli.
Conclusions: Participants with rAMD were less able than HCs to detect subliminal happy faces, suggesting this phenomenon is mood-independent. These results extend previous research showing that depressed participants have impaired recognition accuracy for briefly-presented happy faces. Continued recruitment in this RDoC study will allow us to validate these preliminary findings and examine neural correlates.

Keywords: Emotional processing, Faces, Depression, Bipolar, Remission
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200. Effects of Depression and HPA-Axis Function on Executive Functions and Affective Processing

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Background: Elevated cortisol levels impair hippocampal mediated verbal memory retrieval in major depressive disorder (MDD), but there is lack of consensus as to whether hyperactivation of the neuroendocrine system impairs prefrontal-mediated executive functions or affective processing.
Methods: Forty-two individuals with MDD and 38 HCs, ages 18-65, completed a Parametric Go/No-go Task and the Facial Emotion Perception Test. Salivary cortisol was measured on the same day at 08:00, 12:00, 16:00, and 21:00 hours. Hierarchical multiple regressions evaluated the effects of cortisol, diagnosis, and their interactions on executive functions and affective processing.
Results: MDD participants had significantly higher average cortisol levels (MDD: $M = .65$, $SD = .31$; HC: $M = .53$, $SD = .19$; $p = .04$) and poorer sustained attention (all $ps < .02$). In both groups, elevated mean cortisol was associated with faster response times on go ($b = -57.29$, $p = .01$) and inhibitory trials ($b = -58.72$, $p = .04$), as well as greater detection of sad faces ($b = 1.31$, $p = .03$). Higher cortisol was associated with greater detection of anger in MDD ($b = 1.43$, $p = .04$) but not HCs ($b = -1.06$, $p = .382$). Cortisol was unrelated to set-shifting, cognitive control, or the processing of happy or fearful faces.
Conclusions: Though unrelated to higher-order executive functions, elevated cortisol predicted sustained attention, which

may reflect hypervigilance. Further, this study suggests that while heightened cortisol globally enhances detection of sad material, the effects of cortisol on sensitivity to anger may distinguish individuals with depression from healthy counterparts.

Keywords: HPA axis, cortisol, executive functioning, affective processing, depression
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201. Age-Related Effects on Response Inhibition in Youth at Familial Risk for Bipolar Disorder

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Background: Altered response inhibition (RI), which contributes to impulsivity, has been proposed as a cognitive endophenotype of Bipolar Disorder (BD). It remains unclear to what extent BD offspring (BO), exhibit altered RI compared to offspring of parents with non-BD psychopathology (NBO) and healthy offspring of healthy parents (HC). Here we examined behavioral performance during an affective RI task among these groups.
Methods: Participants were 32 BO, 24 NBO, and 34 HC between 8-16 years. They performed the CANTAB Affective Go/No go task (AGN), which assesses RI to emotional (positive/negative) words. Age was included as a covariate.
Results: There was a significant main effect of group in commission errors ($F(2,80)=7.01$, $p=.002$), with BO and NBO making significantly more errors than HC ($p=.001$; $p=.01$), but no significant difference between BO and NBO. Analysis of commission errors revealed a significant group by age interaction ($F(2,77)=9.95$, $p>.001$). Correlational analyses revealed that age was negatively associated with performance in BO ($r=-0.67$) but not NBO ($r=-0.15$), or HC ($r=-0.09$), suggesting that younger BO made more commission errors than their NBO ($p=.01$) and HC ($p=.001$) counterparts. Similar patterns of findings were observed in youth without diagnoses or medication. No between-group differences were observed for trial type, reaction times or omission errors.
Conclusions: Findings suggest that younger BO exhibit a deficit in RI to emotional stimuli as evidenced by higher commission errors on the AGN task compared to NBO and HC. Such findings are consistent with evidence supporting altered early-onset RI as a cognitive endophenotype of BD.

Keywords: Offspring of parents with bipolar disorder, Affective go/no-go task, impulsivity, response inhibition
Supported by: 2 R01 MH060952-11

202. Decision-Making Competence and Attempted Suicide

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Background: Impulsivity and cognitive impairments have been identified as part of the suicidal diathesis; however, how these factors may lead to suicidal behavior is yet to be determined.
Methods: Building on advances in behavioral decision research, we used individual-differences measures, the Adult Decision-Making Competence, in 171 older adults to gain insight into the role of decision-making competence in late-life suicidal behavior. We included three patient groups (suicide attempters, ideators, and non-suicidal depressed participants) who had been diagnosed with unipolar non-psychotic major depression, and non-psychiatric controls. We examined separately individuals who had made medically serious (high-lethality) and less serious (low-lethality) suicide attempts, as there is increasing evidence that these subgroups possess distinct cognitive and personality profiles. We used general linear models to examine group mean differences.
Results: Low-lethality attempters were less likely to abort actions for which costs were irrecoverable, i.e. resistance to sunk cost, than psychiatric controls, suicide ideators, and high-lethality attempters. In contrast, high-lethality attempters performed the worst on the cognitively demanding task of conceptualizing the problem at a higher abstract level and ignoring "superficial" differences, i.e. resistance to framing effects, followed by low-lethality attempters and depressed non-suicidal controls, whereas ideators and non-psychiatric controls had the best performance on this task. These significant group differences remained after accounting for demographic characteristics, global cognition, and personality factors.
Conclusions: Deficits in some aspects of decision-competence, such as the inability to resist ineffectual courses of action and the susceptibility to be swayed by meaningless differences, are related to suicidal behavior.

Keywords: Depression, Sunk Cost, Decision-Making Competence, Suicide, Cognition
Supported by: NIMH

203. Delayed Recall of Masked Emotional Faces in Suicidal Behavior: Accuracy at the Expense of Speed

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Background: Suicide constitutes a significant public health problem, one whose neuropsychological underpinnings are not

well understood. The role of emotion processing in individuals endorsing suicidal behavior is a promising and relatively understudied area of research.
Methods: Ninety males, 26 of whom endorsed past or current active suicidal ideation and/or actual suicide attempt (mean age: 38.77) and 64 of whom reported no suicidal behaviors (mean age: 35.83), were administered a masked emotional faces paradigm comprised of three epochs: fearful, happy and angry, all masked with neutral faces and randomized to minimize order effects. Following task completion, participants were administered a posttest and instructed to identify which exact faces (same person, same expression) were previously presented.
Results: No differences were observed for number of faces correctly recalled. However, the suicide group took longer to respond to nearly every facial condition, with significant differences observed for Total response time (RT; p=0.05), RT for correctly identified distractors (p=0.03) and RT to Fearful faces (p=0.02). Interestingly, the only faces to which the suicide group responded more quickly than the non-suicide group were Angry, although this difference was not significant.
Conclusions: These results suggest that speed of emotion processing, and not accuracy, differentiated those in our sample who endorsed suicide behavior from individuals who did not. Given the difficulty in accurately determining suicide risk, facial affect discrimination may constitute a sensitive approach for improved risk assessment. Further, these findings suggest target areas for intervention strategies.

Keywords: Suicide, Masked Affect, Risk Assessment, Response Time
Supported by: W81XWH-10-2-0178

204. Affective Processing in Pediatric Bipolar Disorder and Offspring of Bipolar Parents

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Background: Bipolar disorder (BD) is characterized by biased processing of emotional information. However, little research in this area has been conducted in youth with BD and at- risk individuals. The goal of this study was to determine whether children with BD displayed comparable or more severe manifestations of this bias relative to offspring with BD.
Methods: The sample (N=64 children and adolescents) included 18 individuals with BD and with a family history of mood disorder (13.7±2.51 years, 8 males), 13 unaffected BD offspring (11.56±3.18 years, 6 males), 10 affected BD offspring suffering from psychiatric disorders (11.34±2.97 years, 5 males), and 23 healthy controls (HC-12.78±3.08 years, 8 females). All participants performed the Affective Go/No-Go (AGN) and Rapid Visual Processing (RVP) tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Results: Relative to HC, individuals with BD responded faster to correct trials and committed an elevated number of commission errors across all affective conditions of the AGN task. By contrast, affected BD offspring performed the AGN task as accurately as HC but their response times to affective stimuli were shorter. RVP performance was comparable across groups.
Conclusions: In line with previous findings children with BD displayed inefficient processing of emotional information. The faster response times to affective stimuli in BD offspring may constitute a marker of vulnerability to BD. Multimodal studies are needed to characterize the neural correlates of emotional information processing in pediatric BD and high-risk individuals.

Keywords: Pediatric Bipolar Disorder, Affective Processing, Bipolar Disorder, Affective Go/No-Go (AGN), Rapid Visual Processing (RVP)

205. Emotional Intelligence and Subliminal Presentations of Social Threat

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Background: The ability to rapidly process emotional facial cues is crucial for successful social interactions. Altered brain responses to subliminal (i.e., backward masked) facial cues have been associated with several forms of psychopathology. However, even healthy individuals vary widely in their capacity to regulate and understand their own emotions and those of others, a construct known as Emotional Intelligence (EI). The aim of this study was to identify the brain networks associated with EI during masked presentations of fearful (withdrawal threat) and angry (approach threat) faces.
Methods: Fifty-four 18-45 year olds (50% females) underwent blood oxygen dependent (BOLD) functional magnetic resonance imagining (fMRI) while viewing images of fearful and angry faces, each presented for 20ms and "masked" immediately by a neutral face for 100ms, minimizing or preventing explicit visual perception. Participants also completed measures of EI.
Results: EI was only associated with prefrontal cortex (PFC) responses to approach cues of social threat. For masked angry faces higher EI correlated negatively with bilateral activation in the dorsolateral superior frontal gyrus and the inferior frontal gyrus, whereas no association between EI and brain activation in response to masked fearful faces was found.
Conclusions: Higher EI was correlated with reduced activation within the dorsolateral PFC in response to subliminal presentations of approach cues of social threat, in particular anger. Higher EI may be associated with automatic adaptive responses that facilitate rapid decision-making in response to social cues indicative of potential threat. EI may be an important dimension for understanding the neurocircuitry underlying some forms of psychopathology.

Keywords: emotional intelligence
Supported by: W81XWH-09-1-0730

206. The Adverse Effect of Chemotherapy on the Developing Brain

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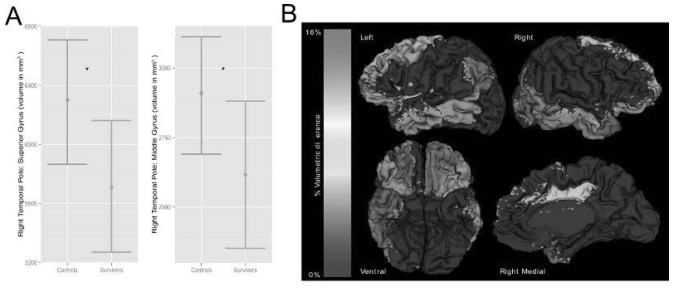
Background: Over 90% of children with acute lymphoblastic leukemia (ALL) will be cured of their illness. Unfortunately, the chemotherapy treatment necessary to eradicate leukemia is also associated with long-term side effects: between 40 – 60% of ALL survivors experience cognitive impairments, including deficits in working memory, cognitive flexibility, inhibitory control, and sustained attention. We sought to determine whether these cognitive changes may be the result of alterations in brain development.
Methods: ALL survivors (n=18) and age- and sex-matched controls (n=13) between 8 – 18 years old underwent 3T structural MRI (data collection ongoing). T1-weighted anatomical scans were processed using the CIVET pipeline. We performed volumetric measurements of gray matter and white matter for each lobe on both sides, and performed measurements of cortical thickness, surface area and volume. We performed linear regression models with age and group as explanatory variables. P-values were corrected for the number of false discoveries.
Results: Total gray matter was significantly reduced in ALL survivors compared with controls ($p < 0.05$). Cortical volume deficits in ALL survivors were evident across various regions in the cerebrum (see figure). There was also a general trend across various brain regions of significantly reduced cortical thickness in ALL survivors.
Conclusions: Our results show that chemotherapy is neurotoxic to the developing brain. Using MRI, we may be able to uncover the mechanism by which chemotherapy results in cognitive impairments, providing the foundation for research into treatment modifications.



Keywords: brain development, acute lymphoblastic leukemia, neuroimaging, chemotherapy
Supported by: Canadian Institutes of Health Research – Institute of Cancer Research, the Canadian Cancer Society, C17 Council, Pediatric Oncology Group of Ontario and Garron Family Cancer Centre at the Hospital for Sick Children, and SickKids Department of Psychia

207. Chronic Therapeutic Ketamine Use Associates With Metabolic Changes: Mitochondrial Proliferation and Respiratory Complex1 Deficiency in Buccal Tissue and Inferred Hepatic Stat3/stat5 Signaling

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Background: Recent animal data suggests that genetically fixed baseline complex 1 activity in the mitochondria substantially determines the clinically effective dose of ketamine when used as an anesthetic. Conversely, systemic cytosolic MTOR activation produced by ketamine may theoretically down regulate mitochondria metabolism. The interactions between innate and acquired mitochondrial regulation in the individual patient treated with ketamine are unknown.
Methods: 10 patients provided buccal tissue samples after treatment with ketamine (mean dose 12.7 mg/kg po) for a mean 51 month duration. An overlapping cohort of 7 patients provided serology corresponding to principle component deviations observed in NR1 -/- knockdown mice: fibrinogen, apolipoprotein A1, and IGF1.
Results: Aggregate complex 1 activity (2.86 +/- 2.78) in patients was significantly lower (t. = 4.59, p. =0.00) than control aggregates (6.9 +/- 2). Aggregate citrate synthase levels in patients (26.5 +/- 13) were significantly higher (t. =2.91, p. =.02) than the control aggregate (15 +/- 7.5). Discontinuation of ketamine in one patient normalized complex 1 activity after 3 weeks. Serum fibrinogen/IGF1 (3.5, N=7, t = 2.2, p. = 0.035) and apoliproteinA1/IGF1 (1.82, N=5, t= 4.4, p.=0.005) was significantly higher in patients than non-clinical population norms.
Conclusions: Chronic therapeutic human ketamine use associates with metabolic changes in multiple peripheral tissues. The implications of these changes are unknown.

Keywords: ketamine, mitochondria, pain, depression, NMDA

208. Buried Legacy? An Analysis of Psychiatric Toxicity of Pre-chloroquine Anti-malarials

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Background: The toxicity of synthetic anti-malarials such as primaquine, chloroquine, and mefloquine have been well documented. Their side effects range from hemolytic anemia in the case of primaquine to psychiatric disturbances in the case of chloroquine and mefloquine. The toxicity profiles of their pre-WWII predecessors, however, have received relatively little attention. Atabrine, a synthetic anti-malarial developed by German industrial chemists in the 1920s and 1930s, proved invaluable for malaria control among Allied and Axis troops alike.
Methods: An extensive review of peer-reviewed literature was conducted.
Results: Atabrine, however, was not without its own toxicity issues. As its use expanded, first in far-flung colonial outposts and subsequently in Asian and European theatres, reports began to emerge about unexpected psychiatric toxicity.
Conclusions: Despite these warnings, their central role as anti-malarials continued throughout the Second World War. This

presentation will examine the factors that spurred their widespread use despite a growing number of contemporary reports that recommended cautious use among high-risk individuals.

Keywords: Drug toxicity, Atabrine, synthetic anti-malarials, psychosis

209. Association Between Leptin Gene (LEP) and Antipsychotic-induced Weight Gain (AIWG): New Results and Meta-analysis

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Background: Antipsychotics are commonly used to treat major psychiatric disorders. However, antipsychotic-induced weight gain (AIWG) has remained a major concern. Several replicated findings suggest an association between AIWG and a promoter variant of the leptin gene (-2548G/A LEP or rs7799039). The present study aims to evaluate this association using data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), and by subsequent meta-analysis.
Methods: We imputed the SNP rs7799039 in the CATIE-GWAS and investigated its associations with: percentage of BMI change and weight gain categories using ANCOVA in R. We included (n=189) CATIE participants of European ancestry using stringent criteria for our AIWG studies, treated with olanzapine, risperidone and quetiapine for approx. 87 days on average. For our meta-analysis, we performed PubMed searches using 'leptin weight gain polymorphism' keywords. All computations were performed using R package meta.
Results: As for the CATIE sample, no associations could be detected between rs7799039 and percentage of BMI change and weight gain categories. For our meta-analysis, we included eight studies. We saw no significant effect ($p>0.05$), however heterogeneity was significant across samples (chi sq.=17.12,p=0.0166). However, significant associations for rs7799039 and AIWG appeared to be driven by long-term studies (minimum three months on average) conducted in Asian populations.
Conclusions: Overall, we noticed no effect of leptin variants on AIWG. Positive rs7799039 – AIWG associations were available for long-term studies in Asians. For others, study duration ranged between 6-8 weeks, which maybe relatively short to detect effect of rs7799039 on AIWG.

Keywords: AIWG, antipsychotics, schizophrenia
Supported by: CIHR

210. Effect of Antipsychotics on Intestinal Motility in Zebrafish (Danio rerio) Larvae

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Background: Atypical antipsychotics are efficient but exhibit anticholinergic side effects, including constipation. This serious side effect is associated with some atypical drugs. In the current study, we developed an in vivo assay to evaluate the effect of different antipsychotics on intestinal motility in zebrafish larvae.
Methods: Five days post fertilization zebrafish larvae (Casper strain) were used to access the intestinal peristaltic activity through optical microscopy. The samples were imaged using a stereomicroscope before drug exposure (0-5 min; basal) and after drug treatment (7-12 min and 14-19 min; treatment). Clozapine, haloperidol and risperidone diluted in DMSO were used. Analysis was performed by counting intestinal contractions observed along the fourth, sixth and eighth myotomes.
Results: Clozapine significantly reduced ($n=7$; $p<0.05$) the intestinal contractions per minute (mean±SEM; basal: 1.02 ± 0.13; 7-12 min: 0.69 ± 0.14; 14-19 min: mean 0.19 ± 0.08). Both haloperidol and risperidone had no effect on intestinal motility (basal: 1.19 ± 0.05; 7-12 min: 1.2 ± 0.03; 14-19 min: 1,2 ± 0.03; n = 7), (basal: 0,98 ± 0,08; 7-12 min: 1,06 ± 0,06; 14-19 min: 0,97 ± 0,04; n=7), respectively.
Conclusions: Intestinal motility assay using zebrafish larvae appears to be a sensitive model to identify gut side effects caused by drug exposure. Among the antipsychotic drugs tested, only clozapine significantly reduced the intestinal motility. The assay confirms the effects observed during the clinical use of clozapine.

Keywords: antipsychotics, constipation, side effects, zebrafish, clozapine
Supported by: CNPq

211. Using the Metabolome to Understand the Cardiovascular Effects of Mental Health Treatments

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Background: Atypical antipsychotics (AAPs), which increase cardiovascular risk have become more common in schizophrenia and bipolar disorder. Metabolomics, the characterization small molecules, may elucidate AAP associated changes and allow for the identification of metabolic pathways and biomarkers in related to AAP metabolic effects.
Methods: An untargeted metabolomic approach using Liquid Chromatography coupled with Mass Spectrometry (LC-MS) was employed to investigate the metabolite profiles of age, gender and race matched patients with bipolar disorder and schizophrenia treated with AAPs or Lithium. Univariate and multivariate analyses were performed to identify significant differences between these groups.
Results: A total of 83 bipolar and 50 schizophrenia subjects (67% female and 81% Caucasian) were included with an average age of 43.0 ± 12.1 years. Serum samples (50 BP-AAP, 33 BP-Li, 50 SP-AAP) were processed in both LC-MS positive and negative modes. Paired Least Squared Discriminate Analysis (PLS-DA) showed separation between groups, with the most important being retinal, the oxidized form of retinol (R^2=0.75, p=0.007). Vitamin A metabolism, which involves retinal, has been linked to insulin resistance and was higher in BP patients on AAPs as identified by post-hoc anova.
Conclusions: We identified a distinct AAP metabolomic profile, highlighting retinal, which is involved in a metabolism pathway previously linked to insulin resistance. A targeted metabolomics approach is needed to confirm these findings . Identifying metabolite differences involved in glucose regulation are positive findings

given AAP metabolic side effects, and may deliver useful biomarkers which could be used when employing personalized medicine strategies in mental illness.

Keywords: Metabolomics, Schizophrenia, Bipolar Disorder, Atypical Antipsychotics
Supported by: NIMH R01 MH082784; NCATS UL1RR024986

212. Effect of Putative OCD Risk Gene BTBD3 on Behavior in Mice

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Background: The BTBD3 gene was identified as genome-wide significant in the trio portion of the first obsessive-compulsive disorder (OCD) GWAS. However, the role of BTBD3 in regulating behavior is unknown. Here, we studied the role of BTBD3 in modulating behaviors relevant to OCD in mice.
Methods: For both experiments, male and female BTBD3 wild-type (WT), heterozygous (HT) and knockout (KO) mice were pair-housed by genotype and were assessed in this behavioral battery: the open field, the splash test, and the prepulse inhibition (PPI) paradigm. Mice were assessed weekly for barbering. Experiment 1: 136 mice were assessed as described. Experiment 2: 270 mice were treated with 10 mg/kg/day fluoxetine, 20 mg/kg/day desipramine, or vehicle for fourteen weeks. Mice were assessed in the behavioral battery four weeks into drug treatment. Data were analyzed using repeated measures ANOVAs except barbering, which was assessed using chi-square and Kaplan-Meier survival curves.
Results: Open field: BTBD3 KO mice were hyperactive. HT and KO mice showed reduced frequency of and time spent rearing. Splash test: HT and KO mice exhibited more frequent, but shorter grooming bouts. PPI: BTBD3 genotype had no effect. Barbering: HT and KO barbered more than WT mice. Fluoxetine but not desipramine reduced barbering in WT and HT but not KO mice.
Conclusions: BTBD3 expression modulates behaviors relevant to OCD. Barbering behavior was selectively reduced by chronic fluoxetine treatment in WT and HT mice, lending predictive validity for this phenotype as OCD-like. We are currently assessing the neurobiological mechanisms of BTBD3's role in behavior.

Keywords: OCD, BTBD3, GWAS, Animal Models
Supported by: BRF to SD

213. Whole-exome Sequencing in Obsessive-compulsive Disorder Identifies Rare Mutations in Immunological Pathways

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Background: Studies of rare variations have successfully characterized molecular pathways within regions of the genome that confer risk for developmental neuropsychiatric disorders. To date, no published whole-exome sequencing studies have been reported in obsessive-compulsive disorder (OCD). We sequenced all coding regions of the genome in 20 sporadic cases of OCD and their unaffected parents.
Methods: To explore the functional molecular correlation between genes with non-synonymous DNMs finding in OCD probands, a protein-protein interaction (PPI) network was generated based on interactome database of physical direct pair-wise molecular interactions. To further investigate the relevance of the genes with non-synonymous DNMs we applied the Degree-Aware Disease Gene Prioritization (DADA) analysis, ranking these genes with DNMs based on their relatedness to a set of previously identified genes in a recently published OCD meta-analysis (Taylor, 2013) and the first OCD GWAS (Stewart et al., 2013). In addition, we performed a pathway analyse with the genes of PPI network.
Results: Altogether, 19 de novo variants (11 missense, 1 nonsense and 7 silent) in 17 trios were validated. The rate for coding de novo variation per base was 2.51 X 10–8. Of these, WWP1, AP1G1 and CR1 were each highly and independently interconnected with other non-neighboring genes ("brokers") in the PPI. BAMBI had the highest rank in the DADA analysis following by WWPI and AP1G1, brokers genes in the PPI.
Conclusions: Pathway analysis suggested an enrichment of genes involved in immunological systems and central nervous system. Furthermore, nearly all genes harboring DNMs in the present study are expressed in the human brain and are implicated in synaptogenesis and neuronal apoptosis.

Keywords: single-nucleotide variation, de novo mutation, exome sequencing, obsessive-compulsive disorder, genetics
Supported by: FAPESP

214. Identification of Novel Candidate Genes in Canine Noise Phobia – A Model for Human Phobias

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Background: Noise phobia (NP), a fear of loud noises, is a severe anxiety disorder in dogs, which may result in panic like behaviour. It provides a natural animal model for human phobias. NP is common (20-40%) in many breeds with high heritability (h2 0.56) estimates but its genetic background remains unknown.
Methods: We aimed to discover the genetic cause by a genome wide association analysis. We focused on German Shepherds because the breed is popular and presents sufficient phenotypic variation in NP. We used our validated owner-completed anxiety questionnaire to create a categorical NP phenotype and genotyped altogether 310 German Shepherds (GS) (86 cases and 224 controls) to map the NP locus.
Results: We found a genome widely significant association in a 4 Mb region at CFA20 harboring several interesting candidate genes. Targeted capture and resequencing of the associated region from 39 dogs revealed several disease segregating variants that were enriched in two promising candidate genes.
Conclusions: Further validation and functional characterization of variants in a larger GS cohort and other breeds should implicate the causative gene. This study will improve the understanding of

the genetic background of noise phobia, and at best reveal a new candidate gene for human anxiety and help in developing a model for human phobias.

Keywords: anxiety, genetics, dog, phobia
Supported by: ERC Starting Grant

215. Study on the Role of Genetics in Pain Perception amongst Pain Patients with a History of Depression

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Background: Many studies have shown that patients with depression tend to display higher pain perception.
Methods: 435 pain subjects with reported history of depression across 20 clinical research sites in the US. 221 with high pain perception and 214 control with low pain perception matched for age, gender and race. Subjects completed a Pain VAS rating their perception of pain (0-10). Low pain perception was 1-4 and high pain perception 7-10. Subjects were genotyped using Taqman® SNP Genotyping Assays (Life Technologies, Carlsbad, CA). It consists of a panel of 12 SNPs of genes in the mesolimbic reward pathway. These include:5HT2a, 5-HTTL, COMT, ANKK1/DRD2, DRD1, DRD4, DAT, DBH, MTHFR, OPRK1, GABA-A receptor gamma2, and OPRM1.
Results: A chi square test using SPSS V21 found 5-HTTL(rs140701) and DBH (rs1611115) as the only SNPs that have significant association with pain perception. {(5-HTTL: Dominant model (G/G vs. G/A-A/A) p=<0.001, {DBH: Dominant model (C/C vs. C/T-T/T) p= 0.014). Further analysis using a binomial logistic regression found that the combination of G/A & A/A variations of 5-HTTL are more associated with subjects with high pain perception and a history of depression compared to those with low pain perception and a history of depression. p=0.0001,OR=2.178. Also, combination of C/T & T/T variations of DBH was found to be associated with subjects with high pain perception and a history of depression compared to those with low pain perception and a history of depression. p=0.014, OR=1.636.
Conclusions: This study suggests that 5-HTTL (rs140701) and DBH (rs1611115) may play a role in high pain perception experienced by patients with depression.

Keywords: Depression, Genetics, Pain perception
Supported by: Proove Biosciences

216. Variation in Endocannabinoid Signaling Modulates Frontoamygdala Connectivity, Fear Regulation, and Anxiety in Mice and Humans

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Background: The endocannabinoid system has been implicated in modulating affective and cognitive processes. We examined the impact of endocannabinoid signaling on frontoamygdala circuitry, fear regulation, and anxiety utilizing genetic variation in Fatty Acid Amide Hydrolase (FAAH), the main catabolic enzyme of the endocannabinoid anandamide. We hypothesized that the rs324420 (C385A) polymorphism, which leads to lower FAAH levels and higher levels of anandamide, would enhance frontoamygdala connectivity and fear regulation.
Methods: We measured frontoamygdala connectivity in humans using resting-state fMRI and in knock-in mice using tract tracing. We assessed Pavlovian fear conditioning and extinction in both humans and mice. Finally, we examined trait anxiety in human subjects and anxiety-like behaviors in mice.
Results: Human A-allele carriers showed increased functional connectivity between the subgenual vmPFC and the bilateral amygdala, but no difference in connectivity between the amygdala and the dorsal ACC. Knock-in mice had increased anterograde but not retrograde tracts between the homologous infralimbic cortex and the basolateral amygdala and no connectivity differences between the amygdala and prelimbic cortex. Human and rodent A-allele carriers showed significantly enhanced fear extinction and diminished anxiety measures.
Conclusions: We found consistent evidence across humans and mice that variation in endocannabinoid signaling alters brain circuitry, fear regulation, and anxiety symptoms. Mutant allele carriers displayed superior fear extinction, less anxiety-related behavior, and greater frontoamygdala connectivity than wild-type subjects. Mouse model experiments revealed specific directional neurocircuitry changes, with enhanced top-down connectivity in mutant allele carriers. These results represent a potential mechanism linking endocannabinoid signaling to anxiety regulation.

Keywords: Endocannabinoids, Anxiety, Connectivity, FAAH, cross-species
Supported by: NIHGM07739; NIHEY007138; NIHMH079513; NIHMH060478; NIHNS052819

217. Amiloride-sensitive Cation Channel 2 Genotype Variant Affects the Emotional and Cardiovascular Response to a Carbon Dioxide Panic Challenge

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Background: The molecular substrates involved in panic attacks, the core symptom of panic disorder (PD), are still largely unknown. Recently, an association between PD and two variants in the amiloride sensitive cation channel (ACCN2) gene was found. This work was based on a previous study, in which the rodent homologue ASIC1a was identified as important player in detecting pH changes and eliciting fear behavior to CO_2 exposure. However, in humans, the relationship between changes in brain pH and the ACCN2 gene, as done in rodents by CO_2 exposure, has not been investigated yet. Here, we examined this link between the previously shown two ACCN2 gene variants and differential CO_2 sensitivity in healthy volunteers and PD patients.
Methods: 184 PD patients and 106 healthy volunteers underwent an inhalation with 35% CO_2. Negative affect was assessed using fear and panic symptom ratings. In healthy volunteers, additional cardiovascular physiological measurements were obtained. Genotyping was performed on saliva samples. Data were analysed using univariate ANOVA.
Results: rs10875995 was significantly associated with higher fear scores in PD patients and with an increase in systolic as well as diastolic blood pressure in healthy subjects. Subjects homozygous for the T-allele showed a heightened reactivity to CO_2. Furthermore, a trend towards a rs685012 genotype effect on fear scores was found in PD patients.
Conclusions: Genetic variants in the ACCN2 are associated with differential sensitivity to CO_2 in PD patients as well as healthy volunteers, making ACCN2 a promising candidate for future research to improve current treatment options.

Keywords: Panic disorder, CO2, ACCN2, ASIC1a

218. Is There an Association Between the Serotonin Receptor 2A Polymorphisms and Obsessive-Compulsive Disorder: A Systematic Review of the Literature

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Background: Due to the heterogeneous nature of obsessive-compulsive disorder, the underlying genetics of the disorder remain unclear. Clinically, serotonergic dysfunction is implicated in OCD. Evidence is pointing towards examining genetic associations of OCD with polymorphisms in the promoter region of the gene coding for the serotonin receptor 2A (HTR2A).
Methods: A review of all published studies cited in PubMed, MedLine, and Embase, using the search terms "OCD" and "HTR2A" or "serotonin polymorphism".
Results: Out of 232 publications identified, only 13 studies examined the association. Two genetic variants have been found to be significantly associated with OCD: -1438G/A (rs6311) and 516C/T (rs6305). The A allele of rs6311 has been linked to OCD in both adults and adolescents, in those with early onset, but results were inconsistent. There is some evidence that the effect may be sexually dimorphic, specific to females. The C allele of rs6305 was found to be associated with OCD, however this has yet to be replicated. Some studies failed to see any association with either SNPs. Another SNP that was repeatedly tested in relation to OCD was 102T/C (rs6113), with no positive results.
Conclusions: Despite the fact that only a few studies have examined the relationship between HTR2A polymorphisms and OCD, there is promising evidence that the -1438G/A SNP may confer risk to developing OCD. Many studies failed to examine the association by sex, age of onset and symptom severity, all of which should be considered in future studies and may be the key in replicating findings.

Keywords: Obsessive-Compulsive Disorder, HTR2A Gene, Serotonin Polymorphisms, Genetic Association

219. Using Genetic Markers to Compare Obsessive-Compulsive and Related Disorders

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Background: Dissecting the clinical heterogeneity and genetic architecture of the obsessive-compulsive and related disorders (OCRD) represents a valuable strategy to identify more homogeneous subgroups for study. The frequently comorbid disorders in this group include obsessive-compulsive disorder (OCD), hoarding disorder (HD), trichotillomania (TTM), skin picking disorder (SPD), and body dysmorphic disorder (BDD). A recent heritability study suggested two distinct underlying liability factors for these disorders, one for OCD, BDD and HD, and a second for TTM and SPD. We investigated the following OCD candidate genes in patients with OCRD: BDNF, COMT, DRD2, GRIN2B, SLC1A1, HTR1B, and HTR2A.
Methods: Genotyping was performed using the Taqman assays in our Toronto OCD sample, consisting of 216 OCD patients (117 OCD without HD/BDD, 99 OCD with HD/BDD, 167 OCD without TTM/SPD, 32 OCD with TTM/SPD) and 345 healthy controls. We performed two distinct comparisons using Pearson chi-square test (SPSS v20.0) to examine differences in allelic and genotyping distributions across the separate groups. The first compared OCD without HD/BDD to a combined OCD with HD/BDD sample and a second was done similarly with TTM/SPD.
Results: Two markers across the HTR2A gene were nominally associated with general liability to OCD in both of the two OCRD subgroups, while a marker each across the BDNF and HTR1B genes was uniquely associated with HD/BDD in our OCD sample but not with the TTM/SPD subgroup.

Conclusions: These results support the notion that OCRD share similar and distinct genetic factors. Larger and well-characterized samples are warranted to replicate these preliminary findings.

Keywords: Obsessive-compulsive and related disorders, Genetics, Phenotypes, Compulsivity
Supported by: CIHR Postdoctoral Fellowship

220. Genetic Correlates of the Homocysteine Risk Pathway for Alzheimer's Disease: A Genome-Wide Interaction Study

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Background: Observational studies have proposed elevated circulating homocysteine levels as a risk factor for Alzheimer's disease (AD). Homocysteine levels are easily modifiable using available treatments. However, while some clinical trials have reported benefits from homocysteine-lowering interventions on AD-related cognitive and clinical outcomes, others have shown no improvement or deterioration. These inconsistent and at times contradictory results could be due to an interaction of genetic factors with homocysteine levels. Here, using a genome-wide interaction study design, we searched for SNPs that interact with homocysteine levels to predict established biomarkers of AD-related atrophy (hippocampal and entorhinal volumes).
Methods: Analysis was performed on available ADNI-1 data (http://adni.loni.usc.edu/) (healthy elderly=185, mild cognitive impairment=284, AD=130). We conducted genome-wide SNP-by-plasma-homocysteine interaction analyses while controlling for age, gender, education, diagnosis, intracranial-volume and the first three principal components of genetic data (ethnic stratification). Model-robust estimates of standard errors were used to correct for potential inflation of the false-positive rate due to model misspecification in gene-environment-wide interaction studies.
Results: Rs7905675, which mapped to the TFAM gene (encoding a key activator of mitochondrial transcription), showed a near genome-wide significant interaction with plasma-homocysteine levels predicting entorhinal volume ($P=5.04\times10^{-8}$). The same interaction was also predictive of hippocampal volume ($P=1.35\times10^{-5}$) and cognitive function, as indexed by ADAS11 test (P=0.04).
Conclusions: The interaction between rs7905675 genotype and circulating homocysteine levels may explain why homocysteine-lowering treatment could be beneficial for some people and harmful for others. Our findings have immediate implications for pharmacogenetically-informed interventions targeting the homocysteine pathway for the prevention and treatment of AD.

Keywords: Homocysteine, Alzheimer's disease, Genome-wide gene-environment interaction study, Imaging-genetics
Supported by: CIHR

221. Translocator Protein (18kDa) rs6971 Is Associated with Markers of Cerebrovascular Disease and Neuroinflammation

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Background: Chronic neuroinflammation is a pathological hallmark of Alzheimer's disease (AD). The translocator protein (TSPO) is up-regulated in activated microglia and is thought to be a marker for neuroinflammation; studies have found that TSPO and its ligands affect processes related to inflammation and neurovascular health that are implicated in AD etiopathology. The TSPO rs6971 polymorphism determines TSPO ligand binding in the brain, however, no study has examined how this variant affects imaging or plasma biomarkers in clinical samples.
Methods: From the Religious Orders Study / Memory and Aging Project (ROS/MAP), 850 postmortem brains were analyzed for amyloid angiopathy and the presence of cerebral infarcts. From the Alzheimer's Disease Neuroimaging Initiative (ADNI-1), 744 subjects underwent structural neuroimaging for the detection of white matter hyperintensities and a subset of 520 subjects were analyzed for plasma inflammatory protein biomarkers. All subjects were genotyped for rs6971.
Results: In ROS/MAP, rs6971 AA genotype was associated with lower risk for micro cerebral infarcts (p=0.036), and in ADNI-1, the same AA genotype was associated with reduced white matter hyperintensity burden (p=0.015). In the ADNI-1 plasma biomarker subset, the same rs6971 AA subjects showed significant diagnosis-dependent changes in both VEGF (p=0.004) and TNFalpha ($p=1.9\times10^{-5}$).
Conclusions: Our results suggest that TSPO rs6971 genotype may affect multiple phenotypes related to cerebrovascular disease and inflammation. Given that TNFalpha and VEGF both have promising potential as therapies targeting inflammatory processes and neurovascular deficits, molecular subtyping according to TSPO genotype may be important for identifying at-risk individuals for future treatment trials.

Keywords: Neuroinflammation, Alzheimer's Disease, White Matter Hyperintensities, Postmortem Cerebral Infarcts, Translocator Protein (TSPO)
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222. Dopamine Genetic Polymorphisms Predict Spatial Working Memory Function in Normal Four-Year Old Children

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Background: Several psychiatric disorders linked to altered dopamine (DA) signalling, including schizophrenia and ADHD, are also characterized by impairments in working memory. While it is well established that DA function plays a key role in working memory in adults, the early developmental origins of this relationship remain largely unknown. Our goal was to examine the association between five functional variants of DA system genes and spatial working memory in a normal cohort of pre-school children.
Methods: The current sample consisted of 214 children, assessed at age four, participating in a longitudinal study of early brain development (The MAVAN Project). General linear models assessed whether 5 functional DA system variants (DAT1 9-repeat, DRD4 7-repeat, DRD2-141C Ins/Del, DRD2 Taq1A C (A2), and COMT $Val^{58}Met$) predicted performance on a standardized computer-based test of spatial working memory using CANTAB.
Results: Strikingly, three of the five DA gene variants were significantly associated with spatial working memory performance in these children. The 7R allele of DRD4 and the Del allele of DRD2-141C predicted more test errors, while the Met/Met genotype of COMT predicted fewer test errors (at p=.025 in all cases).
Conclusions: Dopamine genetic variation associates with spatial working memory ability, a critical component of normal and abnormal cognitive function, as early as age 4. Given that deficits in both working memory and DA functioning are frequently observed in adults with psychiatric disorders, further follow-up will determine whether these early developmental findings are key intermediate phenotypes to later psycho-pathology.

Keywords: Dopamine, Working memory, Pre-school, Polymorphism
Supported by: Canadian Institutes of Health Research (CIHR)

223. Genetic Influences on Brain Plasticity: First Results of the ENIGMA Plasticity Working Group

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Background: The brain is changing throughout life. Since brain plasticity is positively associated with cognitive functioning, and aberrant plasticity is genetically implicated in diseases such as schizophrenia, genes associated with brain plasticity may aid in identifying genetic pathways related to healthy and abnormal brain development.
Methods: Compared to the extensive research on the heritability of brain structure, there has been relatively little study of the heritability of structural brain change. To address the issue of generalisability and robustness of longitudinal heritability, we combined heritability estimates from several longitudinal twin cohorts. Here we present preliminary results from two cohorts (BrainSCALE; 179 children of age 9, interval 3 years and UMCU twins; 182 young adults of mean age 29, interval 5 years). In each cohort, changes in global brain volumes were estimated from longitudinal Magnetic Resonance Imaging data using the FreeSurfer pipeline. Heritability was estimated using the OpenMx package in R by comparing similarities between members of monozygotic and dizygotic pairs.
Results: Change in global brain volume, lateral ventricle volume, total cerebellar volume were consistently heritable in children (heritability 36%, 30%, 60%, respectively) and adults (heritability 36%, 30%, 73%, respectively). Global white matter volume change and cortical volume change were heritable in children (69%; 34%) but not significantly so in adults.
Conclusions: Change in global brain volumes is consistently heritable, and can serve as a phenotype for a GWA study. Age is an important factor as not all brain changes will be heritable, or driven by the same genes throughout life.

Keywords: Imaging, Genetics, Plasticity, heritability

224. Exposure to Adversity in Pre-School Aged Children, Glucocorticoid Receptor Gene Methylation and Behavioral Outcomes

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Background: Growing evidence demonstrates linkage between early adversity and glucocorticoid receptor gene (*NR3C1*) methylation; a key regulator of the hypothalamic-pituitary-adrenal axis. No prior work has considered the contribution of *NR3C1* methylation to childhood behavior problems. The current study examined links between adversity, *NR3C1* promoter methylation, and behavior problems in preschoolers.
Methods: 184 (*n*=74 with child welfare documentation of moderate-severe maltreatment in the past six months) participated in the gene methylation study; *n*=171 (*n*=71 moderate-severe maltreatment) participated in the behavioral problems assessment. Children ranged in age from 3-5 years and were racially and ethnically diverse. Structured record review and interviews assessed adversity; parental report and interviews determined internalizing and externalizing behaviors. Region 1_D, 1_F, and 1_H *NR3C1* promoter methylation was measured via sodium bisulfite pyrosequencing from salivary samples.
Results: Composite adversity measures were positively correlated with methylation at exons 1_D and 1_F in the *NR3C1* promoter. Individual stress measures were significantly associated with a several CpG sites in these regions. *NR3C1* promoter methylation at exons 1_D and 1_F was positively associated with internalizing (r = .17, $p < .05$ and r = .23, $p < .01$ respectively), but not externalizing, behaviors. *NR3C1* methylation significantly mediated the association between early adversity and internalizing behaviors.
Conclusions: Early adversity is correlated with *NR3C1* promoter methylation and *NR3C1* methylation is associated with internalizing behaviors in young children. *NR3C1* promoter
methylation may be a mechanism by which adverse exposures influence the bio-behavioral outcomes associated with early adversity.

Keywords: Gene, Methylation, Maltreatment, Children, Internalizing behavior
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225. Transcriptional Signatures Specific to Individual Human Genomes can be Identified in Pluripotent Stem Cells and are Stable Cellular Traits Throughout Life

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Background: Advances in genomic, imaging, and iPSC technology now make it possible to generate billions of data points describing the genomes and molecular behavior of cells from many humans across the range of cellular biology. Dynamic, mechanistic perspectives defining the unique biology of individual human genomes within these growing waves of data will empower personalized medicine.
Methods: We have generated a unique experimental resource pairing pluripotent stem cell lines and postmortem brain tissue from the same individual human donors. We use a new approach including a matrix factorization algorithm, CoGAPS, to interrogate deep RNA sequencing data across these systems.
Results: We dissect the temporal dynamics of transcription during early development at an unprecedented resolution. Remarkably, we identify genome-specific transcriptional signatures present in pluripotency and early differentiation. These signatures are stable across: >5 years maintenance in different laboratories, mRNA measurement technologies, diverse growth conditions, multiple iPSC lines from individual genomes, and the fibroblasts that gave rise to the iPSC lines. This indicates that these transcriptional signatures are genetic in origin. We hypothesize that these signatures are present in all cells of a human and that their diversity underlies risk for complex disease. We explore this possibility by interrogating RNA-seq data from mature human brain tissue with transcriptional signatures observed in pluripotent cells from the same individual human.
Conclusions: Here we describe a framework to study the unique biology of individual human genomes in pluripotent cells, drawing concrete parallels between in vitro and in vivo biology that will help guide in vitro modeling of human biology and disease risk.

Keywords: Pluripotent Stem Cells, Human Brain, Transcriptional Signature, Individual Genome, iPSC Model
Supported by: Lieber Inst. for Brain Development

226. Early Trauma Modulates the Correlation between DNA-Methylation in the Transcription Start Site and Expression of Glucocorticoid-responsive Genes

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Background: Environmental factors especially early in life, (e.g. early trauma, ET) can contribute to stress-related disorders by modification of epigenetic marks including DNA methylation. We and others have previously shown that CpGs altered by ET are often located outside of the core promoter. In this study, we want to further elucidate the functional interaction of DNA methylation and ET on gene transcription.
Methods: Gene expression (Illumina HumanHT-12 v3 array), DNA methylation (Illumina 450K-methylation array) and ET (Childhood Trauma Questionnaire, CTQ) were measured in the Grady trauma cohort, which consists of a highly traumatized, primarily African American urban population with low socioeconomic status.
Results: We selected 10 glucocorticoid responsive genes from gene expression array experiments in peripheral blood. For these, we identified CpGs located around the promoter that strongly correlate with gene expression ($p<0.001$). ET did not have a main effect on DNA methylation of these functional sites in any of these loci. However, in five genes, ET significantly moderated the correlation between promoter CpGs methylation and gene expression (N=320). For example, for SGK1 there was a significant ($p=0.0017$) difference in the correlation coefficient in non-traumatized r = -0.311 vs traumatized individuals r = -0.574.
Conclusions: ET moderates the correlation between promoter-CpGs methylation and expression of glucocorticoid-responsive genes. Further experiments to identify the ET-associated mechanisms that alter the correlation (e.g. epigenetic effects in enhancer elements) are currently on going.

Keywords: Epigenetics, DNA methylation, Early trauma

227. ULK4 Genetic Variants Associate with risk of Autism and Its Gene Expression in Human Postmortem brains

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Background: ULK4 is crucial for brain development, and has been associated with risk for schizophrenia in European ancestry population. We examined the association of common genetic variants at ULK4 with autism.
Methods: The study subjects included 273 autism case-parent triads in Han Chinese population, and SNPs were genotyped on Illumina HumanHap CNV370K chip in the genomic region of ULK4 (upstream and downstream 100kb) were selected for analysis. Transmission Disequilibrium Test was performed to test for association of individual SNPs with risk of autism. We also examined the association of genetic variants with ULK4 gene expression in the prefrontal cortex of postmortem human brain.
Results: Thirteen SNPs (59 SNPs were tested) showed nominal significant association with autism ($p<0.05$). The most significant associations were observed at rs17066958 at ULK4||TRAK1 ($p=0.00025$) and rs1716975 in ULK4 ($p=0.00071$). These SNPs were in strong linkage disequilibrium ($r2>0.8$) with a number of SNPs in this locus. We further found that SNP rs1716975 was strongly associated with ULK4 gene expression ($p=4.94E-07$) in prefrontal cortex. This SNP along with other two strongly expression-associated SNPs rs105201 ($p=1.77E-08$) and rs2272077 ($p=4.94E-07$) are non-synonymous and regulate RNA splicing according to bioinformatics investigation. The genetic association of ULK4 rs1716975 variants with gene expression was in consistent trends in human postmortem brain of different life stage and race.
Conclusions: We found evidence for association of ULK4 genetic variants with risk of autism in Han Chinese population, and the autism risk associated SNPs may have potential regulatory effect on ULK4.

Keywords: Autism, ULK4, Genetic Variants, Postmortem brains
Supported by: the Major State Basic Research Development Program of China (973 Program, No. 2012CB517901 and No. 2010CB529601) and Hunan Graduate student research innovation project (No. CX2012B095)

228. Association and Gene-gene Interactions Study of Reelin Signaling Pathway Related Genes with Autism in Chinese Han Population

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Background: The etiology of autism remains unclear due to its nature of a complex polygenic inheritance disease. Reelin signaling pathway has been reported to be involved in the brain development in human embryo stage. Our study was to explore the association and gene-gene interactions of 6 genes in reelin signaling pathway with autism in Chinese Han population.
Methods: Genotyping was performed in 430 autistic children fulfilled DSM-IV-TR criteria for autistic disorder and 1074 healthy controls. Single marker case-control association analysis and haplotype-based case-control association analysis were conducted after the data was screened. Multifactor dimensionality reduction (MDR) was applied to test the gene-gene interactions.
Results: Neither single marker nor haplotype association test found any significant difference between autistic group and control group after permutation test of 1000 rounds. The 4-locus MDR model (comprising rs614373, rs1858782, rs634500 and rs1924267 which belong to *RELN* and *DAB1*) was considered as the best model for gene-gene interaction (cross validation consistency=9/10, testing balanced accuracy=0.5821, *P*=0.001).
Conclusions: The results indicated that interaction between *RELN* and *DAB1* might increase risk of autism in Chinese Han population. Furthermore, it can also be inferred that *RELN* would be involved in the etiology of autism through interaction with *DAB1*.

Interactions identified by multifactor dimensionality reduction			
Model	Testing balanced accuracy (%)	Cross validation consistency	P value
rs1858782	0.5175	9/10	0.568
rs7799082 -rs634500	0.5608	3/10	0.751
rs614373-rs1858782-rs634500	0.5619	9/10	0.019
rs614373-rs1858782-rs634500-rs1924267	0.5821	9/10	0.001
rs1799821-rs1924267-rs6667829-rs7799082-rs6943822	0.5142	4/10	0.636

Keywords: Autism, Reelin, Gene-Gene interaction
Supported by: the National Basic Research Program of China:2012CB517901

229. A Genome Wide Association Study of Hoarding Behaviours in a Community-Based Sample of Children and Adolescents

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Background: Hoarding disorder (HD) is a new addition to the DSM-5. Little is known about hoarding particularly during childhood and adolescence when many individuals with HD report that their symptoms began. In particular, although hoarding is heritable (~50%) the specific risk genes are still unknown. To help identify these genes, we conducted a genome-wide association study (GWAS) on hoarding behaviours in a large community sample of children and adolescents.
Methods: DNA and ratings of hoarding behaviours based on the Toronto Obsessive-Compulsive Scale (TOCS) were collected on 17263 children and adolescents visiting a Science Museum. A total score for hoarding behaviours (-6 to +6) was calculated based on ratings from TOCS items related to excessive acquisition and difficulty discarding. From salivary DNA, we genotyped 5366 unrelated individuals of Caucasian descent using the Illumina HumanCoreExome and OMNI1 beadchips. 9,598,793 imputed and genotyped SNPs that passed standard quality control (QC) metrics were included in the analysis. Association was tested using linear regressions for the continuous hoarding total score using principal components to control for population structure.
Results: Eighty-nine percent of the sample passed QC (N = 5056). Although no genome-wide significant hits were identified in this analysis, we identified SNPs with P values as low as 2.1x10-6 (λ = 0.99).
Conclusions: Although we did not reveal any genome-wide significant findings, this analysis is the first step in a pipeline which will examine rare variants, gene-set and pathway approaches.

Keywords: hoarding, genetics, children and adolescence, GWAS, community sample
Supported by: CIHR MOP-106573; MOP – 93696

230. A Genome Wide Association Study of Quantitative ADHD Dimensions in a Community-Based Sample of Children and Adolescents

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Background: ADHD is a heritable childhood-onset disorder characterized by inattention (IA) and hyperactivity/impulsivity (HI). Genome-wide association studies (GWAS) to date have failed to pinpoint the genetic risk variants underlying ADHD; however, using dimensional quantitative traits in large community samples may help boost power for GWAS studies of ADHD. To this end, we conducted a genome-wide association study (GWAS) of IA/HI traits in a large community sample of children and adolescents.
Methods: DNA and ratings of ADHD traits based on the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN) were collected on 17263 youth visiting a Science Museum. From salivary DNA, we genotyped 5366 unrelated Caucasians using the Illumina HumanCoreExome and OMNI1 beadchips. 9,598,793 imputed and genotyped SNPs that passed standard quality control (QC) metrics were included in the analysis. Association was tested using linear regressions for the quantitative IA and HI z-scores separately using principal components to control for population-structure.
Results: 89% percent of the sample passed QC (N = 5066). Phenotypically, IA and HI were positively correlated ($R = 0.66$, $p < 0.01$) and as a result shared the same top SNP: rs1087989 (IA: $p = 1.8x10\text{-}6$ & HI: $p = 7.7x10\text{-}7$; $\lambda = 0.99$) on chromosome 12 near KCNC2 (MAF = 0.3) which is involved in synaptic transmission.
Conclusions: Both IA and HI traits may be associated with a similar genetic risk variant involved in neuronal communication. These analyses are the first step in an analysis pipeline which will examine rare variants, gene-set approaches.

Keywords: ADHD, GWAS, Traits, Community Sample, Children and Adolescents
Supported by: CIHR MOP-106573 and MOP – 93696

231. The Relationship between Academic Performance and Academic-related Boredom: The 5-HTTLPR Gene Polymorphism as a Moderator

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Background: In previous research, studies that examine the effects of genes on academic-related emotions are largely lacking. the present study sought to examine the moderating effects of the promoter of the serotonin transporter (5-HTTLPR) gene polymorphism on the relationship between students' academic performance and their academic-related boredom.
Methods: In a sample of 420 Chinese high school students, we collected data about their academic-related boredom and academic performance. In addition, students' DNA was extracted from cheek cells. Polymerase chain reaction (PCR) was performed to amplify the DNA fragment.
Results: The results indicated that students with the genotype of the 16/16 repeat in their 5-HTTLPR gene were more likely to be influenced by academic performance on their academic-related boredom.
Conclusions: Our findings suggested that the functional polymorphism of the 5-HTTLPR gene moderated the relationship between academic performance and academic-related boredom.

Keywords: 5-HTTLPR, Academic-related boredom, Chinese
Supported by: National Natural Science Fund of China

232. 1q21 Microduplications in Two Pediatric Patients with Neurodevelopmental Disorders

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Background: Copy number variations (CNVs) are risk factors for neurodevelopmental anomalies. 1q21 duplications have specifically been reported in association with hallucinations, schizophrenia, and autism spectrum disorder (ASD), among other disorders.
Methods: We conducted genetic analysis with the goal of detecting CNVs in patients and their immediate family members who came to the NIH for screening as part of the childhood onset schizophrenia study. Symptoms and family history were ascertained by chart review, video recorded interviews, and structured interview reports.
Results: Two pediatric patients were found to have 1q21.1 duplications. Patient NSB3207 was diagnosed with ASD upon discharge; her brother, also with the CNV, was diagnosed with anxiety upon structured interview. NSB3207's father carries the 1q21.1 duplication and is asymptomatic. Her mother does not carry the duplication and does not have any mental health diagnoses. Patient NSB3127 came to the NIH diagnosed with psychotic disorder not otherwise specified, attention deficit hyperactivity disorder, oppositional defiant disorder, and separation anxiety disorder. She inherited her CNV from her mother, who has diagnoses of depression, anxiety, and a recorded "axis I diagnosis," and self-reports Tourette's syndrome and ASD. The proband's father was diagnosed with mood, anxiety, and alcohol disorders, and has a recorded "axis I diagnosis." He self-reports having ASD and was not found to have a CNV.
Conclusions: The phenotypes expressed by carriers of the 1q21 duplication illustrate the pleiotropy of the duplication, and the diagnoses of non-carrier family members highlight the complexity of identifying a sole, definitive genetic cause for neurodevelopmental disorders.

Keywords: Copy number variation, Neurodevelopmental disorders, Genetics

233. Independent Replication of DRD4 x Maternal State Interaction on Child Behavior Problems (CBCL), and Mediation by 7 mo Infant Temperament: Analyses in a Pilot Longitudinal Cohort of Mother-Infant Dyads

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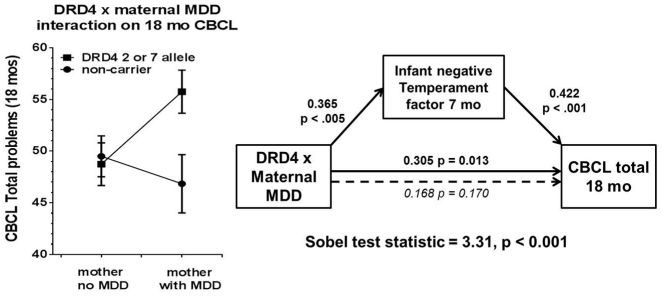
Background: The DRD4 VNTR has been associated with child behavior problems in gene x maternal insensitivity interactions in European and American cohorts of preschoolers; with 7-repeat allele associated with greater problems. We attempted to replicate and expand these findings by examining trajectories from early mother-infant dyadic interactions (7 mos) in a longitudinal cohort.
Methods: We are collecting a longitudinal cohort of mother-infant dyads (268 families recruited to date) with psychological and/or behavioral assessments at 6wks, 4mo, 7mo, 12mo, 15mo, 18mo, and 36mo. A latent variable "Negative Infant Temperament" was constructed from maternal report (IBQ) and behavioral coding (Distress, Negative Affect in Still Face paradigm at 7 mo), Achenbach CBCL was assessed at 18 mo. Maternal and infant genotype on DRD4 was obtained using PCR. A 65 family sample with complete DRD4 genotype, Infant Temperament, and 18 mo CBCL was used.
Results: Infants carrying 7- or 2-repeat DRD4 allele who had mothers meeting criteria for postpartum depression had greater behavior problems (CBCL) at 18 mo, but not non-carriers (interaction F=4.4,p<.05; beta=.305,p=.013). DRD4xMaternal depression was also associated with Infant Negative Temperament (beta=.365,p<.005), which mediated the effect on 18 mo CBCL (Sobel=3.31, p<.001)
Conclusions: These initial analyses replicate DRD4 x maternal state interaction in an independent cohort. The interaction effect on CBCL was seen at 18 mos, and was mediated by infant (7 mo) measure of negative temperament. Data collection is ongoing in this longitudinal cohort.



Keywords: DRD4 DRD4, Replication, Gene x Environment, Child Behavior Problems, Infant Temperament
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234. Gene-Environment Interactions with Childhood Maltreatment and 5HTT and 5HTTLPR

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Background: The serotonin transporter (5HTT) gene has been implicated in many mental disorders including with anxious-aggressive behavior in children. The 5HTT gene has also been reported to have environmental effects on mental disorders such as depression, however this interaction not been studied in relation to anxious-aggression in children. We hypothesized that 5 HTT rs25531 and the 43 base pair insertion deletion (5HTTLPR) would interact with a history of maltreatment and would be significantly associated with outcomes of anxiety-aggression in children.
Methods: Data was analyzed from our child aggression database with the children genotyped and information regarding maltreatment and anxious-aggression data. This included 166 participants. Information about Anxiety-aggression scores were taken from Child Behavior Checklist. Statistics were calculated using SPSS v 19.0. Statistics used included ANOVA and Univariate analysis.
Results: The 5HTT rs25531 genotype had a significant effect on Aggression t-score ($p<0.05$)/ Furthermore had a significant interaction with a history of maltreatment ($p<0.001$). The 5HTTLPR was significantly associated with total anxiety ($p<0.05$) but did not have a significant interaction with a history of maltreatment ($p>0.05$).
Conclusions: Maltreatment has a significant interaction with function of the 5HTT gene on anxiety-aggression. Epigenetic modifications at several sites of the 5HTT gene have recently been reported to influence depression phenotypes, thus future work may include examination of these 5HTT modifications and their interaction with maltreatment and the anxious-aggression phenotype in children. We will report the results of our epigenetic findings with anxious-aggressive children.

Keywords: Anxiety-Aggression, Genetics, Serotonin Transporter Gene, Childhood maltreatment
Supported by: Canadian Institute of Health Research Grant

235. Insular Cortex GABA Is Reduced in Trauma-exposed Adults With and Without PTSD and Associated With Posttraumatic Growth

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Background: In a previous investigation using proton magnetic resonance spectroscopy (1H-MRS), we found that adults with posttraumatic stress disorder (PTSD) had less right insular cortex gamma-aminobutyric acid (GABA) than healthy adults, which may be consistent with robust evidence of insula hyperactivity from functional imaging studies of PTSD. In this study, we sought to replicate this finding in a sample including a group of trauma-exposed adults without a history of PTSD. This research

design enables examination of whether low insula GABA reflects disorder-specific changes and/or a consequence of exposure or adaptation to trauma.
Methods: Twenty-three adults with DSM-IV PTSD, 11 trauma-exposed adults without PTSD, and 14 healthy control subjects underwent single voxel 1H-MRS at 3T. GABA was measured in a 12mL right insula voxel using MEGAPRESS spectral editing. Trauma subjects were interviewed using the Clinician-Administered PTSD Scale (CAPS) and completed trauma-related questionnaires including the Life Events Checklist and Posttraumatic Growth Inventory (PTGI).
Results: Compared with healthy controls, both trauma-exposed and PTSD subjects had significantly lower insula GABA/Cr levels ($F(2,44)=4.99$, $p=.01$; Tukey's HSD<.05). Within trauma and PTSD subjects, GABA/Cr was significantly negatively correlated with PTGI scores ($r(22)=-0.55$, $p=.008$). In contrast, neither CAPS symptom scores nor lifetime trauma load was significantly associated with insula GABA/Cr.
Conclusions: These findings suggest that low insular cortex GABA is a consequence of traumatic stress exposure rather than a correlate of the PTSD clinical syndrome. An association with posttraumatic growth raises the possibility that insula GABA reduction may reflect positive personal adaptations that occur in the aftermath of trauma.

Keywords: posttraumatic stress disorder, magnetic resonance spectroscopy, GABA, insular cortex, trauma
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236. Reduced Serotonin Synthesis after Pharmacological Treatment of Social Anxiety Disorder

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Background: Neuroimaging trials suggest that pharmacological treatments of social anxiety disorder (SAD), including selective serotonin re-uptake inhibitors (SSRI) and neurokinin-1 receptor (NK1R) antagonists, exert their anxiolytic effects, at least partly, through reduced amygdala activity. The neurochemical underpinnings of anxiolyis, however, are not well understood. Here we investigated serotonin synthesis rate in the amygdala of SAD patients before and after pharmacological treatment.
Methods: Eighteen SAD patients were randomized to receive double-blind treatment for six weeks with either an SSRI (citalopram; n=6), NK1R antagonist (GR205171; n=6), or placebo (n=6). Serotonin synthesis rate capacity was assessed before and after treatment in the patients and 17 age and sex-matched healthy controls (HC; only scanned once) using positron emission tomography imaging with the radiotracer [^{11}C]5-HTP. The Liebowitz Social Anxiety Scale (LSAS) was used to index symptom severity.
Results: Before treatment, SAD patients had significantly higher serotonin synthesis rate than HC within the right amygdala (MNI x,y,z: 24,6,-16; $Z=3.64$, $P_{FWE}=0.007$), and synthesis rate within this region correlated positively with LSAS scores ($r(16)=0.55$, $P=0.019$). Conjunction analyses revealed that treatment with citalopram and GR205171, but not placebo, decreased serotonin synthesis rate in an overlapping cluster within the right amygdala (MNI x,y,z: 30,4,-28; $Z=2.45$, $P_{unc}=0.007$). Decreased serotonin synthesis rate within this cluster correlated positively with symptom improvement ($r(16)=0.56$, $P=0.016$).
Conclusions: The results are consistent with anxiogenic effects of serotonin in the amygdala. Contrary to the notion that SSRI-treatment of anxiety enhances deficient serotonergic neurotransmission, our results suggest that anxiolysis could be achieved through decreased serotonin synthesis in the amygdala.

Keywords: Anxiety disorders, Serotonin, SSRI, PET imaging, Treatment study
Supported by: the Swedish Research Council, the Swedish Brain Foundation, Riksbankens Jubileumsfond – the Swedish Foundation for Humanities and Social Sciences, the Swedish Research Council for Health, Working Life and Welfare, GlaxoSmithKline

237. Oylethanolamide Modulates Human Neural Responses to Food Stimuli in Obesity

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Background: Obesity has emerged as a leading health threat and major risk factor for type 2 diabetes, cardiovascular disease, and hypertension. The neurobiological basis of overeating remains insufficiently known, hampering sufficient intervention strategies. Here we investigate oleoylethanolamide, an agonist of PPAR-α. It has been implicated in weight regulation in animals but its respective role in humans is still unclear.
Methods: Associations between plasma oleoylethanolamide, BMI and associated neurobiological impact (fMRi response to food stimuli) in 21 obese patients (BMI≥30) and 24 controls were investigated. We hypothesized that oleoylethanolamide interacts with BMI and fMRI response to food stimuli and may be affected in obese patients.
Results: Associations between oleoylethanolamide and BMI differed significantly depending on whether subjects were obese or not ($P=0.02$). For obese individuals, oleoylethanolamide showed a trend towards a positive correlation with BMI ($P=0.06$, $rho=0.42$) while this relationship was inverse for controls ($P=0.07$, $rho=-0.34$). We observed significant interactions between oleoylethanolamide and obesity on food-related brain activation in cortical areas associated with reward processing and interoceptive signaling ($P=0.009$). fMRI-investigation of food-craving suggests that identified brain areas may be involved in suppressing 'liking' of food, in non-obese subjects.

Conclusions: Oleoylethanolamide modulates motivation of intra-gastric feeding, possibly through normalization of PPAR-α-dependent vagal feedback to the brain in rodents. This supports its homeostatic function for regulating dietary fat intake via vagal-nigro-striatal pathways. Our study suggests that oleoylethanolamide mediates reward-associated neural processes and this signaling plays an important role for hedonic regulation of food-craving and obesity in humans. It may be a valuable target for developing novel anti-obesity drugs.

Keywords: Oleoylethanolamide, Food-craving, Obesity, Human, Novel treatments

238. Increased Striatal Dopamine $_{D2/3}$ Receptor Availability and its Association with Executive Function in Adults with Phenylketonuria

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Background: Executive function (EF) deficits have been reported in adults with phenylketonuria (PKU), an inborn error of metabolism, despite early diagnosis and continuous treatment. This is thought to relate to cerebral monoaminergic deficits as a result of residual elevated plasma phenylalanine (pPhe) levels.
Methods: We measured *in vivo* striatal dopamine $D_{2/3}$ receptor ($D_{2/3}R$) availability using [^{123}I]iodobenzamide (bolus/continuous infusion) and a brain-dedicated single photon emission computed tomography (SPECT) system in 15 adults with PKU and 12 healthy controls (HC). We used the computerized Amsterdam Neuropsychological Tasks to test EF in the PKU group prior to imaging.
Results: Mean pPhe levels were 706.5 ± 373.4 µmol/l in the PKU group. The mean striatal $D_{2/3}R$ availability was significantly higher (13%; p = 0.032) in the PKU group than in the HC group, reflecting a hypodopaminergic state. No significant correlations between pPhe levels and EF were observed. However, $D_{2/3}R$ availability correlated positively with error rate during a working memory task (r = 0.49, p = 0.037), and with error rate during a cognitive flexibility task (r = 0.57, p = 0.016). No such associations were observed for an inhibitory control task.
Conclusions: These results suggest that increased striatal $D_{2/3}R$ availability is associated with worse EF performance in adults with PKU. To the best of our knowledge, this is the first study to show associations between EF and cerebral dopaminergic systems in PKU, consistent with the monoamine deficit hypothesis.

Keywords: Executive Function, Phenylketonuria, Dopamine, SPECT
Supported by: Dutch Brain Foundation KS2012(1)-31

239. Plasma Apolipoprotein E and Severity of Suicidal Behavior

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Background: Apolipoprotein E (ApoE) serves as a ligand for the low-density lipoprotein receptors and participates in cholesterol transport. Low cholesterol levels are associated with suicidal behavior. However, very few studies have assessed Apolipoprotein E in relation to suicidal behavior.
Methods: A total of 100 suicide attempters were assessed with Karolinska Suicide History Interview and Karolinska Interpersonal Violence Scale (KIVS) for age of onset of suicidal behaviour, number of earlier suicide attempts and exposure to interpersonal violence. Plasma ApoE levels were measured with immunonephelometric method.
Results: Earlier age of onset of suicidal behaviour and higher number of earlier suicide attempts were significantly correlated to higher plasma ApoE levels in suicide attempters. Results remained significant after adjustment for age. Exposure to interpersonal violence showed a significant positive correlation with ApoE (rho=0.25, p=0.04). Broken down by gender, the correlation between ApoE and childhood trauma was significant only in male suicide attempters (rho=0.57, p=0.006).
Conclusions: Plasma ApoE levels may be related to severity of suicidal behaviour.

Keywords: suicide, Apolipoprotein E, childhood trauma, age of onset, lipids
Supported by: Swedish Research Council

240. Revisiting Microglia Activation in Psychiatric Illnesses: A Postmortem Approach

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Background: A significant number of studies have provided evidence about microglial abnormalities in major psychiatric diseases. Increased markers of microglial activation have been reported in schizophrenia, mood disorders and suicide. Nevertheless, the identified pattern of activation is distinct from that observed in classical inflammatory processes such as trauma, stroke and neurodegenerative diseases. The present study utilized morphological criteria to analyze microglial activation in the orbitofrontal cortex of people with varied psychiatric illnesses compared to non-psychiatric controls
Methods: Immunohistochemistry for Iba1 with enhanced sensitivity using nickel DAB was employed in the orbitofrontal cortex of psychiatric patients (N = 56) and non-psychiatric controls (N =

44). Morphological analysis consisted of separating white and grey matter and classifying microglia according to their morphology in normal resting, intermediate and fully activated states
Results: All 3 states of microglial activation were observed in both control and psychiatric patients. The number of fully activated microglia was very low in all cases, coinciding with the absence of overt inflammatory processes as determined by histological analyses. A number of patients in both control and psychiatric groups presented hypertrophied microglia of significant size localized mostly surrounding sulci and vascular structures. No specific association was found between microglia at different stages of activation and psychiatric condition
Conclusions: While several microglial abnormalities have been identified in psychiatric conditions, our results suggest that a classical pro-inflammatory profile defined as M1 type may not underlie the pathophysiology of mental illness. The specific microglial processes associated with disease pathology remain to be defined

Keywords: Inflammation, Depression, Suicide, Cytokines, cardiovascular disease
Supported by: R01 MH097676

241. Overweight Women but not Men Have Lower Tryptophan Levels

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Background: Obesity has been shown to be associated with elevated kynurenine (KYN), tryptophan (TRP), and ratio of kynurenine to tryptophan (KYN/TRP), a marker of indoleamine 2,3-dioxygenase (IDO) activation, and chronic inflammation. We investigated sex differences in obesity and KYN and TRP levels in healthy adults.
Methods: Healthy male and female adults (N = 1000) from Munich, Germany, were classified as normal weight and overweight/obese based on BMI. Plasma samples were obtained to measure KYN and TRP level. ANCOVA was used to determine the relationship between weight status and KYN, TRP, and KYN/TRP with adjustment for age and sex, followed by post-hoc Tukey test for significant findings.
Results: Our sample (N = 1000) consisted of 490 men and 510 women. There was no significant relationship between overweight/obesity and TRP ($F = 0.017$, $p = 0.90$), KYN ($F = 1.43$, $p = 0.23$), and KYN/TRP ($F = 1.15$, $p = 0.28$) after adjustment for age and sex in our sample of healthy individuals. Overweight/obese women had significantly lower TRP than overweight/obese men ($p = 0.02$) but there was no significant difference in TRP between women and men who were not overweight/obese.
Conclusions: The results of our study, conducted in a large sample of healthy individuals, suggest that the previously described association between obesity and KYN may not be present if psychopathology is controlled for. Previous studies have shown that obese women have increased depression whereas obese men have decreased depression. Our findings suggest that decreased TRP levels may be associated with depression in obese women and that treatment with TRP may be useful to alleviate depression in this group.

Keywords: Obesity, kynurenine, tryptophan, depression
Supported by: K18MH093940 (PI Postolache) ; NORC grant P30 DK072488 (Shuldiner, Postolache); MIRECC, Baltimore, MD; VISN 19 MIRECC, Denver, CO (Postolache); DIG-AFSP (Postolache and Rujescu; equally contributed and share senior authorship)

242. Early Life Stress Affects Stress-related PFC Dopamine Activity in Healthy Adults, But Not in Individuals with Psychotic Disorder

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Background: Early life stress may have a lasting impact on the developmental programming of the dopamine (DA) system implicated in psychosis. Early life stress could promote resilience by calibrating the prefrontal stress-regulatory DAergic neurotransmission to improve the individual's fit with the predicted stressful environment. Aberrant reactivity to such match between proximal and distal environments may, however, enhance psychosis disease risk.
Methods: We explored the combined effects of childhood adversity and adult stress by exposing 12 unmedicated individuals with a diagnosis of non-affective psychotic disorder (NAPD) and 12 healthy controls (HC) to psychosocial stress during an [18F] fallypride positron emission tomography. Childhood trauma experienced before the age of 12 was assessed retrospectively using a questionnaire.
Results: In healthy individuals, severity of childhood trauma was positively associated with the spatial extent of mPFC DA activity under acute psychosocial stress ($b=7.23$, $t(11)=3.06$, $p=.016$). Additionally, a significant negative association between childhood trauma and subjective stress response emerged in this group ($b=-.9$, $t(11)=-2.5$, $p=.03$), with higher early trauma correlating with lower subjective stress response to the task. In the NAPD group,

childhood trauma was not associated with the spatial extent of the tracer displacement in mPFC (b=-1.22, t(11)=-0.67), nor with the subjective perception of stress (b=.12, t(11)=.27, p=.79).
Conclusions: The findings reveal a potential mechanism of neuroadaptation of prefrontal DA transmission to early life stress, and suggest its role in resilience and vulnerability to psychosis.

Keywords: Psychotic disorder, Stress, Dopamine, PFC, Childhood adversity
Supported by: ERC-2012-StG, project 309767 – INTERACT

243. Psychotic Reactivity to Social Stress in the Real World Is Associated with Prefrontal DA Reactivity to Experimental Stressor

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Background: Stress is an important risk factor in the etiology and exacerbation of the positive symptoms of psychosis. Dopamine (DA) has been implicated in the modulation of stress response and assignment of salience to stimuli. The dysregulation of the DA signaling under social stress might result in aberrant salience of social cues, thus giving rise to paranoid ideation.
Methods: This study combined [18F]fallypride PET with an Experience Sampling ambulatory assessment approach to examine the association between the prefrontal DAergic response to experimentally-induced stress and psychotic reactivity to the subjective experience of social stress in daily life of 11 unmedicated patients with non-affective psychotic disorder (NAPD). We performed multilevel regression analyses to test the relationship between prefrontal DA reactivity to experimentally-induced social stress and increased paranoia in response to stressful social contexts in the real world.
Results: Stress-related paranoia in daily life was positively associated with the extent of stress-induced DA activity in the mPFC (b=.0002, t(10)=2, p=0.046). Specifically, NAPD with a more extensive stress-induced prefrontal DA activity endorsed higher paranoia during instances of increased social stress in the real world (b=0.25), relative to their less reactive counterparts (b=-007). Analogously, during the experimental manipulation, increased paranoia in response to the stressor was associated with greater extent of DA activity in the mPFC (b=.001, t(10)=2.8, p=0.037).
Conclusions: These findings point towards a role of the DAergic activity in the mPFC in the modulation of the psychotic reactivity to social stress in the daily lives of individuals with psychotic disorder.

Keywords: Psychotic disorder, Stress, Dopamine, PFC, ESM
Supported by: ERC-2012-StG, project 309767 – INTERACT

244. Decreased Glutamate Concentrations in the Anterior Cingulate Cortex in Schizophrenia as Measured by 7T Magnetic Resonance Spectroscopy

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Background: Convergent lines of evidence indicate that schizophrenia involves alterations in glutamate neurotransmission. While human postmortem and animal-model studies have been critical in achieving this understanding, any definitive testing of existing models requires in vivo demonstration in humans of neurotransmitter system pathology. In this study we measured glutamate-related neurochemical profiles in medicated volunteers with schizophrenia (SZ) and matched normal controls (NC) using proton magnetic resonance spectroscopy (MRS) at 7 T. The regions of interest (ROI) were the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), two regions critically involved in the pathophysiology of the disease.
Methods: Scanning included a scout scan and several spectral acquisitions with ROIs focused on the ACC and DLPFC. For each region, an optimized PRESS scan was conducted at 7T: PRESS (TE1, TE2) = (31, 61) ms for measurement of glutamate, glutamine, NAAG, NAA, GABA, creatine, and choline. MRS data acquisition parameters included TR = 2.5 s, Nave = 256, sweep width = 5 kHz, and number of sampling points = 4096 (scan time ≈ 10 min).
Results: Preliminary results from a sample of N = 22 NC and N = 26 volunteers with SZ indicated lower glutamate in ACC in SZ (NC: 1.09 ± 0.06; SZ: 1.2 ± 0.08; p = 0.006) and no significant difference between the groups in the levels of DLPFC glutamate.
Conclusions: These preliminary results are consistent with previous reports of the levels of neurometabolites in schizophrenia. We intend to expand the sample by scanning additional participants, as well as unmedicated schizophrenia volunteers.

Keywords: schizophrenia, magnetic resonance spectroscopy, glutamate, anterior cingulate
Supported by: 5R21MH093959

245. Sex Differences in the Associations Between Prefrontal GABA and Resistance to Sleep Deprivation

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Background: There are consistent trait-like individual differences in the ability to resist the degrading cognitive effects of sleep deprivation (SD), but few if any reliable biomarkers for this capacity have been identified. The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been implicated in sleep regulation, with patients diagnosed with primary insomnia demonstrating

significant GABA alterations. The objective of this study was to use magnetic resonance spectroscopy (MRS) to examine brain GABA as a potential predictor of resistance to SD.
Methods: Metabolite data were acquired using MEGAPRESS at 3T from medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and occipital lobe (OCC), in healthy adult men (n=20) and women (n=20). MRS and cognitive functioning data were acquired prior to a 30-hour SD challenge. Resistance to SD was determined via hourly administrations of a 10-minute Psychomotor Vigilance Test (PVT).
Results: Participants demonstrated a significant decline in PVT performance during SD, with similar decrements observed across sexes: men performed at 86.5% and women at 84.9% of baseline (pre-deprivation) levels. While no sex differences were observed in OCC GABA, women had higher frontal lobe GABA, in both MPFC and DLPFC, relative to men. However, in men, higher MPFC GABA significantly predicted greater resistance to sleep deprivation on two performance measures ($p<.05$).
Conclusions: These findings suggest frontal lobe GABA, specifically in MPFC, plays an important role in the ability to resist sleep deprivation in men. Assessment of neurochemistry may therefore be useful in predicting and discriminating vulnerable individuals from those who are more resilient to SD.

Keywords: Sex differences, GABA, sleep, frontal, deprivation
Supported by: D12AP00241 (WDK)

246. Occupancy of Dopamine D2 and D3 Receptors by Buspirone: A [11C]-(+)-PHNO PET Study in Humans

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Background: There is considerable interest in blocking the dopamine D_3 receptor (DRD_3), versus the D_2 receptor (DRD_2) to treat drug addiction. However, no selective DRD_3 antagonist isavailable in the clinic. Buspirone,an anxiolytic drug,has been proposed as a potential strategy for addiction as it is suggested that this drug has high *in vitro* affinity for DRD_3, binds to DRD_3 in the brain of living non-human primate and also disrupts psychostimulant self-administration in preclinical animal models. No study has explored the DRD_3occupancy by buspirone in humans.
Methods: We used positron emission tomography (PET) and theDRD_3 preferring radioligand, [^{11}C]-(+)-PHNO, to test the hypothesis that buspironeoccupies(decreases [^{11}C]-(+)-PHNO binding) DRD_3 more than DRD_2.Eight healthy participants underwent [^{11}C]-(+)-PHNO PET scans after administration of placebo,or30, 60, and 120 mg of buspirone(four scans) in a single-blind within-subjects design.
Results: [^{11}C]-(+)-PHNO binding in DRD_2 and DRD_3-rich areas was decreased by the highest (60-120mg), but not the lowest (30mg), doses of buspirone. The maximal occupancy obtained was ~25% in both areas. Plasma levels of prolactin (a DRD_2 marker) correlated with occupancy bybuspirone. Self-reported dizziness and drowsiness increased after buspironeintake but that did not correlate with receptor occupancy in any region.
Conclusions: Overall, the modest occupancy of DRD_2 and DRD_3 even at high doses of buspirone, yielding high levels of metabolites, suggests that buspirone may not be a drug suitable to preferentially block DRD_3 in humans.

Keywords: buspirone, PHNO, dopamine, PET, occupancy
Supported by: R21 DA033515-01

247. Suppressed Serum TSH: A Signal for Cocaine Abuse?

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Background: Despite the cocaine use epidemic, most users remain unidentified and untreated. Cocaine use has been linked to disruptions in hypothalamic-pituitary-thyroid axis signaling including an early report (1992) of blunted TSH response to TRH challenge in cocaine abusers. Cocaine use was also associated with decreased TSH levels in a more recent report (2008). If these results were replicated, it might provide more rationale for inquiring about potential cocaine use in patients with reduced TSH levels.
Methods: Serum TSH levels were obtained from 95 subjects meeting DSM-IV criteria for Cocaine Dependence Disorder per structured interview. Each of the subjects had a positive UDS for cocaine but otherwise was determined to be free of any other lifetime psychiatric or substance use disorder per clinical interview and a comprehensive psychiatric and medical evaluation.
Results: The Cocaine Dependent subjects were primarily male (83.2%) with an average age of 44.5 years, and 70.5% were African-American, 18.9% Caucasian, 8.4% Hispanic, and 2.1% Native American. The mean TSH level was normal (1.42 mIU/liter) but 4.2% had a suppressed TSH level (>0.45 mIU/liter).
Conclusions: The rate of suppressed TSH levels (4.2%) in the Cocaine Dependent Subjects was higher than that generally reported (1.8%) in thyroid disease-free population studies. Several factors may have confounded our results. Relatively higher rates of TSH suppression have been reported in African-American subjects (4%) and 2/3 of our subjects were African-American. However, more than 80% of our subjects were males, and population studies suggest that males (3.5%) have a lower rate of TSH suppression than female (4.5%). Further studies appear indicated.

Keywords: cocaine, thyroid, TSH supression, TSH

248. Functional Consequences of Neurite Orientation Dispersion and Density in Humans Across the Adult Lifespan

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Background: As humans age, a characteristic pattern of widespread neocortical dendritic disruption, coupled with compensatory effects in hippocampus have been shown in postmortem investigations. It is now possible to address age-related effects on gray matter neuritic organization and density in humans using multi-shell diffusion-weighted MRI and the neurite-orientation dispersion and density-imaging (NODDI) model.
Methods: In 45 healthy individuals across the adult lifespan (21-84 years), we used multi-shell diffusion imaging (30 non-collinear directions at 3 b-values: 1000, 3000, 4500 s/mm^2), the NODDI model, and a novel voxel-wise approach (gray matter-based spatial statisitics [GBSS]) to assess the intra-neurite volume-fraction and neurite orientation-dispersion index (ODI) in gray matter. We also determined the functional correlates of variations in gray matter microstructure by obtaining resting-state fMRI and behavioral data.
Results: We found a significant age-related deficit in neocortical-ODI (most prominently in frontoparietal regions), while increased ODI was observed in hippocampus and cerebellum with advancing age. Neocortical-ODI outperformed cortical thickness and white matter fractional anisotropy for the prediction of chronological age in the same individuals. Higher gray matter ODI sampled from resting-state networks with age-related susceptibility (default-mode and visual-association networks) was associated with increased functional-connectivity of these networks, while the task-positive networks tended to show no association or even decreased connectivity. Frontal pole-ODI mediated the negative relationship of age with executive-function, while hippocampal-ODI mediated the positive relationship of age with executive-function.
Conclusions: Our *in vivo* findings align closely with the postmortem data, and provide evidence for vulnerability and compensatory neural mechanisms of aging in gray matter microstructure that have functional and cognitive impact.

Keywords: GBSS, NODDI, Cognitive-Aging, Resting-state fMRI, Gray Matter Microstructure
Supported by: CAMH Foundation, Brain and Behavior Research Foundation, NIMH, CIHR, OMHF

249. Correction for Extracellular Free Water Eliminates Associations of Fractional Anisotropy with Aging and Neurodegenerative Disease

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Background: Standard DTI methodology cannot distinguish between axonal demyelination and increased extracellular free-water (FW). The extent of FW in-vivo has not been well-characterized in healthy aging or neurodegenerative populations. In this study we assess: a) The relationships between FW and aging; b) A comparison of FW between healthy elders, mild cognitive impairment (MCI), and Alzheimer disease (AD) cohorts.
Methods: DTI data were obtained on n=142 healthy controls (HC) recruited in Toronto (ages 18-86) on a 1.5T GE scanner (23 directions,3 repetitions). Of these individuals, 85 were also scanned on a 3T GE scanner (60 directions). We calculated FW and fractional anisotropy (FA) measures, both corrected and uncorrected for FW, using tract-based spatial statistics, and region-of-interest analysis (ENIGMA protocol). Regressions were performed for FA and FW with age. From ADNI2 and ADNIGO data (3T GE scanners, 41 directions) we compared FW and FA in n=100 people with MCI, n=44 people with AD, and n=47 age-matched controls.
Results: We found global statistically significant decreases in FA and FAc, and increases in FW, with increasing age in HC subjects. We identified brain regions significant for standard FA but not for FAc. These results were reproduced at both 1.5T and 3T. The parahippocampus was the white-matter region with the most extensive differences between healthy control and Alzheimer's disease. However, after correcting for FW, no statistically significant trend was found between HC and MCI participants, or MCI and AD participants.
Conclusions: Correction of FA for FW signal is important for populations with neurodegenerative disease. Our finding is that while FA appears to be sensitive to age-related and neurodegenerative changes, correction for FW eliminates these FA differences.

Keywords: Neuroimaging, Diffusion Tensor Imaging, Extracellular Free Water, Alzheimer's Disease, Neurodegeneration

250. Effects of Age and Estrogen Treatment on Cognitive Processing in Postmenopausal Women

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Background: Declining cognitive function with age has been well-documented. Recent evidence suggests that a beneficial effect of estrogen replacement in postmenopausal women (PMW) may be confined to a critical window of years from menopause. This study aimed to better understand how aging influences the effect of estrogen within brain regions implicated in working memory and executive function.
Methods: In a randomized, double-blinded study, younger (n=19; 52+/-2.7 years [mean+/-SD], range 47-56) and older (n=16; 70+/-4.1 years, range 65-79) PMW received placebo or low-dose estrogen treatment. Subjects completed the Nback task while undergoing functional magnetic resonance imaging (fMRI) scanning before, at 2 days (short-term exposure), and at one month (prolonged exposure) after initiation of treatment. fMRI BOLD data were analyzed in SPM8.
Results: At baseline, DLPFC activation was greater in younger than older PMW (p=0.02). After short-term estrogen exposure, DLPFC activation was increased in older PMW (p=0.01), but decreased in younger PMW (p=0.035). However, following prolonged estrogen exposure, DLPFC activation was increased bilaterally in younger PMW (p<0.05), with no sustained effect in older PMW.
Conclusions: Our results indicate a positive effect of short-term estrogen exposure on DLPFC activation in response to a working memory task in older PMW that is not sustained with prolonged estrogen exposure. In contrast, DLPFC activation is initially decreased in younger PMW, possibly due to a learning effect, but significantly increased following prolonged exposure. Taken together, these results support the hypothesis that both aging and treatment duration influence the effect of estrogen in the DLPFC.

Keywords: Neuroimaging, Aging, Estrogen, Postmenopause, Cognition
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251. Predicting Cognitive Decline with Information-Theoretic Clustering of Brain MRI and Blood Tests

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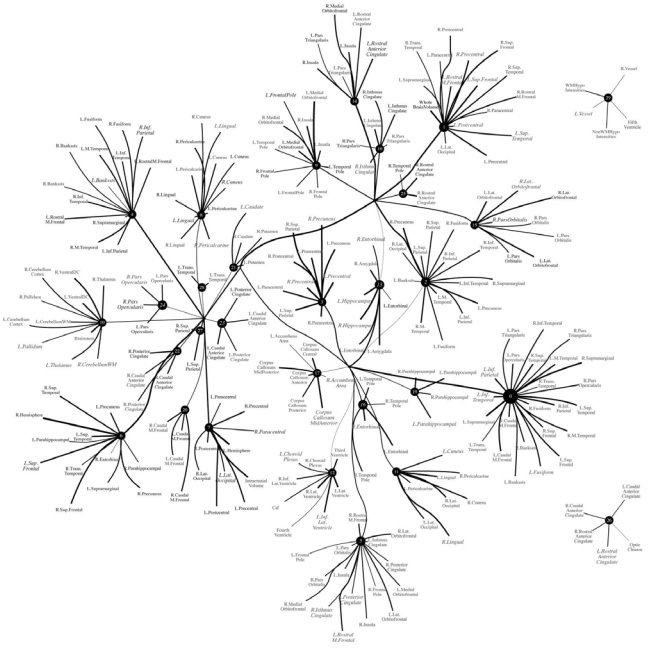
Background: Cognitive decline is debilitating in old age, and is accompanied by brain atrophy and changes in blood markers. Brain volume loss also contributes to the loss of cognitive function in aging.
Methods: We analyzed brain MRI scans in 504 older adults from the Alzheimer's Disease Neuroimaging Initiative (age: 75.0±7.2 years; 198 women, 306 men; education: 15.6±3.0 years; 57 cognitively normal, 351 with mild cognitive impairment, 97 with probable Alzheimer's disease). Cognitive decline was defined as change in Mini Mental State Exam over a one-year follow-up. We also analyzed 196 clinical laboratory measures collected by ADNI as potential biomarkers of clinical decline. We included measures of cardiovascular, immune, inflammation, nutrition, hormones, and many other body functions. We used a novel machine learning method, called CorEx, to find correlations and mutual information among these predictors. We ranked and organized groups of measures based on how well they jointly predicted cognitive decline.
Results: As shown in Figure 1, brain predictors clustered according to known neuroanatomical and functional regions, and in a separate cluster from the laboratory measures. As a group, brain MRI measures outperformed the clinical laboratory measures.
Conclusions: Brain MRI measures may improve prediction of cognitive decline in the elderly. In clinical trials, MRI may help in selecting cognitively intact individuals most likely to develop cognitive decline.



Keywords: Cognitive decline, MRI, Brain, Aging, Blood tests

252. Aerobic but not General Physical Activity in the Healthy Elderly Is Associated with Larger Plasticity in Memory Related Brain Structures and Lower Systemic Inflammation

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Background: Lifestyle factors like physical activity play an important role in preventing neurocognitive decline during aging. To tackle potential mechanisms that may mediate protective effects of physical activity on neurocognitive function, the present study aimed at combining behavioral, immunological and structural as well as functional ultra-high resolution imaging measurements.
Methods: Thirty-two healthy elderly (16 males, mean age 60.94 ± 5.03 SD) underwent a standard neuropsychological testing and a questionnaire based evaluation of their physical activity. Interleukin-6 as well as brain-derived neurotrophic factor were taken from serum blood samples. During scanning at 7 Tesla, subjects performed a blocked associative memory task.
Results: In the absence of general differences between active and inactive subjects, the aerobic fitness group compared to the inactive group showed a better neuropsychological performance that was accompanied by lower interleukin-6 levels. Voxel-based morphometry revealed more gray matter in several temporal regions in the aerobic fitness group and functional analyses showed a) a larger encoding related activation in the precuneus and b) an increased functional connectivity between precuneus and bilateral thalamus, right insula and hippocampus on the one hand and medial prefrontal cortex and right hippocampus on the other hand.
Conclusions: Regular intense physical activity in healthy elderly is associated with a larger plasticity in memory related brain structures and a reduction in systemic inflammation. While being limited due to the cross-sectional nature and sample size, our data suggest a brain mechanism linking peripheral inflammation and risk of age-related cognitive decline that can be protected by aerobic fitness.

Keywords: Aging, Memory, fMRI, IL-6, physical activity
Supported by: Helmholtz grant-Icemed alliance

253. Gabaergic and Glutamatergic Regulation of Fear Recovery

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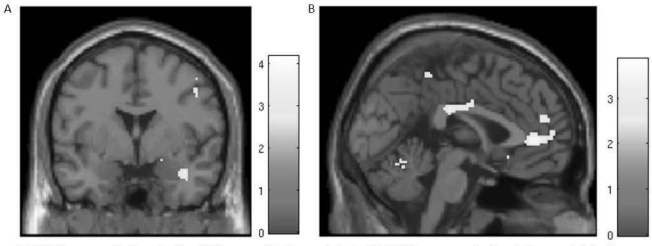
Background: The recall of fear extinction memories has been shown to be impaired in anxiety disorder[1]. Both GABAergic and glutamatergic neurotransmission have been shown to regulate fear in rats[2,3]. The aim of this study was to investigate the involvement of prefrontal GABA and glutamate concentrations in the recovery of fear 24 hours after extinction training.
Methods: Data of 56 right-handed men (mean=21.8 yrs, SD=3.2 yrs) who participated in a multi-modal two-day neuroimaging study were included. They performed a fear conditioning, extinction, and extinction recall paradigm during functional MRI with simultaneous recordings of skin conductance responses (SCR). Fear responses were induced using mild electrical shocks. GABA and Glx concentrations in the dorsal anterior cingulate cortex (dACC) were obtained using GABA edited MRS.
Results: GABA+ and Glx concentrations were quantified relative to creatine concentrations and square-root transformed for statistical analyses ($mean_{GABA}$=0.53, SD_{GABA}=0.06; $mean_{Glx}$=0.56, SD_{Glx}=0.07). SCR data showed recovery of fear responses to the CS+ relative to CS- from late phase extinction training to the early stage of recall. Both dACC GABA+ and Glx levels showed a significant positive correlation with SCR correlates of fear recovery. In a voxel-wise correlation analysis of the fMRI data, GABA+ concentrations were positively associated with BOLD responses in the right amygdala ($MNI_{x,y,z}$=(36,2,-24); P_{FWE}=0.02) while Glx levels positively correlated with activation of the medial prefrontal cortex ($MNI_{x,y,z}$=(4,42,4); P_{FWE}=0.03).
Conclusions: These findings provide first evidence that individual differences in prefrontal GABA and Glx regulate the recovery of fear via distinct nodes in the fear circuitry.



(A) GABA+ concentrations in the dACC are positively correlated with BOLD responses in the right amygdala in the recovery of fear. (B) Glx levels in the dACC are positively correlated with increased BOLD responses in the mPFC.

Keywords: Fear, Anxiety, GABA, Glx, fMRI
Supported by: NWO Veni grant 916.11.037

254. Neural Correlates of Attention Bias in Posttraumatic Stress Disorder: A MEG Study

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Background: Core symptoms of posttraumatic stress disorder (PTSD) include hypervigilance, excessive and inappropriate fear response and attention difficulties. The P300 complex of event-related potentials (ERPs), comprising the P3a and P3b components, was proven as a useful marker of such information processing impairments. The aim of our study was to identify brain regions underlying the P300 response which show differential activity in PTSD patients compared to healthy trauma-exposed controls.

Methods: 15 PTSD patients and 15 healthy trauma-exposed controls participated in a three-tone "oddball" task while being monitored by magnetoencephalography (MEG). They were asked to detect rare target tones while ignoring other frequent tones and infrequent threatening distractors. An adaptive spatial-filter method (SAM beamformer) was applied for source estimation.
Results: Compared to controls, PTSD patients showed hyperactivity in the dorsolateral prefrontal cortex and anterior cingulate cortex in response to frequent sounds, decreased activity in these regions in response to threatening distractors and decreased orbitofrontal activity in response to target stimuli.
Conclusions: Increased frontal activation in response to frequent stimuli may reflect greater resource allocation dedicated to cognitive control mechanisms during routine functioning. This increased frontal activation may therefore account for symptoms of hypervigilance, typical of PTSD. Decreased frontal activation in response to rare stimuli may reflect resultant less available resources dedicated to the identification of, and discrimination between less frequent stimuli, leading to the attention problems reported by patients. A reduction in the frontal processing of infrequent, neutral and threatening, stimuli may lead to diminished regulation and non-specific generalized excessive fear response.

Keywords: PTSD, P300, oddball, MEG, attention

255. Fronto-limbic Functional Connectivity and Emotion Regulation in Obsessive-compulsive Disorder

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Background: Emotion regulation, which may be thought of as the capacity of prefrontal cortex regions to regulate activity in limbic regions, is altered in patients with Obsessive-Compulsive Disorder (OCD). In this study we aimed at comparing the cortico-limbic functional connectivity correlates of emotion regulation between OCD patients and healthy controls.
Methods: Seventy-seven OCD patients and 30 healthy controls completed the Emotion Regulation Questionnaire (ERQ) and underwent a resting-state functional magnetic resonance imaging acquisition. Functional connectivity (FC) of basolateral and centromedial-superficial amygdala (BLA/CMS) with the prefrontal cortex was estimated with a seed-based approach. Scores in the suppression and reappraisal factors of the ERQ were correlated with FC maps.
Results: OCD patients displayed smaller reappraisal ($p<0.001$) and greater suppression scores ($p<0.002$). Significant brain-behavior associations were only observed in healthy controls. Overall, FC between anterior cingulate/medial prefrontal regions and BLA correlated directly with suppression scores and inversely with reappraisal capacity. Conversely, FC between the right ventrolateral prefrontal cortex and right CMS correlated directly with reappraisal scores. None of these findings was observed in OCD patients.
Conclusions: OCD patients make a limited use of cognitive reappraisal, preferentially using suppression strategies to regulate emotions. In healthy controls, suppression strategies are associated with medial prefrontal-BLA connectivity, while reappraisal strategies are associated with right ventrolateral prefrontal-CMS connectivity. This clear segregation between medial and lateral prefrontal connectivity was not observed in OCD, suggesting that emotion regulation alterations of these patients stem from a less definite pattern of cortico-limbic connectivity underpinning prefrontal control of amygdala activity.

Keywords: Fronto-limbic Connectivity, Emotion Regulation, Obsessive-compulsive Disorder, Amygdala, Prefrontal Cortex
Supported by: PI13/01958; CP10/00604

256. Predicting Persistence of PTSD: A Longitudinal Structural and Functional MRI Study

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Background: In about thirty to fifty percent of patients with post-traumatic stress disorder (PTSD) symptoms persist after treatment. While neurobiological research has advanced our understanding of PTSD, little is known about the neurobiology underlying persistence of PTSD.
Methods: Two functional and structural MRI scans were collected from 47 war veterans with PTSD (pre- and post-treatment) and 25 healthy war veterans with a 6-8 month interval. Based on post-treatment symptoms severity a distinction was made between remitted and persistent patients. Hippocampal volume and trauma-unrelated emotional processing was compared for the three groups using repeated measures analyses. Second, logistic regression was used to predict treatment outcome.
Results: Pre- and post-treatment analyses revealed a smaller (left) hippocampal volume, as well as a higher dACC and insula response to negative pictures in persistent patients compared to remitted patients and combat controls at both time points. Prior to treatment, persistent patients showed increased amygdala activation in response to negative pictures compared to remitted patients, but post-treatment amygdala activation was comparable for the three groups. The remitted patients did not differ from combat controls on any of the measures. Finally, dorsal ACC, insula and amygdala activation prior to treatment were significant predictors for persistence of symptoms.
Conclusions: The data presented here suggest that a smaller hippocampal volume and increased activation of the dACC, insula and amygdala may predict poor prognosis for PTSD treatment response. These regions are implicated in trauma-focused therapy and can be considered as markers for persistence of PTSD after treatment.

Keywords: PTSD, treatment, neuroimaging, predictive biomarkers, war veterans
Supported by: Dutch Ministry of Defence

257. Increased Dorsal Cingulum Fractional Anisotropy in Persistent Posttraumatic Stress Disorder

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Background: Post-traumatic stress disorder (PTSD) is a debilitating disorder that has been associated with brain abnormalities, including white matter alterations. However, little is known about the effect of treatment on these brain alterations. To investigate the course of white matter alterations in PTSD, we used a longitudinal design investigating treatment effects on white matter integrity using diffusion tensor imaging (DTI).
Methods: Diffusion tensor and magnetization transfer images were obtained pre- and post-treatment from veterans with (n=39) and without PTSD (n=22). After treatment, 16 PTSD patients were remitted, and 23 had persistent PTSD based on PTSD diagnosis. The dorsal and hippocampal cingulum bundle, stria terminalis, and fornix were investigated as regions of interest. Exploratory whole brain analyses were also performed. Groups were compared with repeated measures ANOVAs for fractional anisotropy, radial, mean and axial diffusivity, and magnetization transfer ratio.
Results: Persistently symptomatic PTSD patients had higher fractional anisotropy in the dorsal cingulum than both combat controls and the remitted PTSD group across both time points. Group by time interactions for FA were found in the hippocampal cingulum, fornix, and stria terminalis, and posterior corona radiata.
Conclusions: Our results indicate that increased fractional anisotropy of the dorsal cingulum bundle is a feature of persistent PTSD. Furthermore, treatment might have different effects on the hippocampal cingulum, fornix, stria terminalis and posterior corona radiata in remitted versus persistent PTSD patients. This study contributes to a better understanding of the neural underpinnings of PTSD and provides evidence for neural markers for treatment outcome.

Keywords: Posttraumatic Stress Disorder (PTSD), Veterans, Treatment, Diffusion Tensor Imaging (DTI), Cingulum Byundle
Supported by: Ministry of Defence, the Netherlands

258. Altered Cerebral γ-Amniobutyric Acid Type A-Benzodiazapine Receptor Binding in PTSD Determined by [11C] Flumazenil Positron Emission Tomography

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Background: Alteration in function of the central of the benzodiazepine (BZD) receptor system is implicated in the pathophysiology of anxiety disorders, including post-traumatic stress disorder (PTSD). Previous positron emission tomography (PET) studies are few and not in agreement, resulting in insufficient understanding of central BZD receptor function contribution to PTSD.
Methods: Twelve medication free patients with a current diagnosis of PTSD, naïve to BZD exposure, and fourteen matched non-traumatized healthy controls underwent a meticulous psychometric assessment and PET scanning, as follows: After injection of 20 mCi of [11C]flumazenil, 60-min dynamic emission images of the brain were acquired. Structural MRI was obtained for co-registration with PET. Binding potential (BP) images were created using the 2-step version of the simplified reference tissue model. BP images were then normalized, smoothed and analyzed using statistical parametric mapping.
Results: Mean [C-11] flumazenil BP was significantly higher in patients with PTSD in a large contiguous cluster comprising the superior and caudal anterior cingulate gyrus and precuneus. No areas were identified where the mean BP was reduced significantly in the PTSD sample relative to the control. Flumazenil receptor BP values positively correlated with clinician administered PTSD scale (CAPS) scores in the left posterior and anterior insular cortex.
Conclusions: This study extends previous findings by suggesting that central benzodiazepine (BZD) receptor system involvement in PTSD is largely mediated by the default mode network. Increased BZD inhibition in this network may be associated with PTSD dimensions of intrusivity, dissociation and hyper-arousal, warranting additional studies.

Keywords: PTSD, PET, GABA-A, DMN
Supported by: NIMH Intramural Research

259. Resting State Functional Connectivity Effects of TMS for Treatment of Generalized Anxiety Disorder

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Background: Transcranial magnetic stimulation (TMS) is a powerful treatment for several psychiatric and neurological diseases, yet its therapeutic mechanism remains unknown. To date, only a handful of studies examined the effect of TMS on resting-state brain connectivity. The current study explored the effects of inhibitory TMS on resting-state connectivity in a group of generalized anxiety disorder (GAD) subjects.
Methods: Resting-state fMRI was collected from 16 individuals with DSM-V GAD, before and after a 6-week course of either sham (n=7) or TMS (n=9) stimulation (right DLPFC stimulation, 1Hz, 90%MT). Independent component analysis (ICA) was used to identify resting-state components. The focus of our analyses was on connectivity within and between the default-mode network (DMN), executive-control network (ECN) and salience network (SN), based on previously hypothesized network abnormalities in GAD. Changes in connectivity metrics were compared between groups, using an ANCOVA (controlling for age, baseline-anxiety and baseline-connectivity). Connectivity changes were also correlated with change in anxiety severity, using partial correlations (controlling for age).
Results: No significant differences were found between the groups in change of connectivity from baseline to end-of-treatment. A moderate correlation that approached significance found between change in anxiety severity (Hamilton-Anxiety total score) and between-network connectivity, for ECN-SN (p=0.1;r=-0.44), and DMN-SN (p=0.11;r=043).
Conclusions: These preliminary results demonstrate a possible relationship between changes in severity of anxiety and between-network connectivity, for ECN-SN (negative correlation) and DMN-SN (positive correlation). Such a relationship was not found for the within-networks connectivity, pointing to a possible mechanism for symptom amelioration. Further research is needed.

Keywords: FMRI, Connectivity, Resting state, TMS, Anxiety
Supported by: Neuronetics LTD

260. The Anatomy of Fear Learning in the Cerebellum: A Systematic Meta-analysis

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Background: Recent neuro-imaging studies have implicated the cerebellum in several higher-order functions, including executive functioning and affect regulation. Preclinical studies have also pointed towards a role of the cerebellum in different forms of associative learning. However, its role in human fear conditioning has so far received limited attention. The current meta-analysis examines the cerebellar contributions to fear learning in healthy subjects.
Methods: Coordinates of cerebellar activity were extracted from published functional MRI studies on fear conditioning. Studies were only included if the presentation of the conditioned stimulus and unconditioned stimulus were separated and if no motor responses were required. We extracted a total of 38 coordinates reported in 22 included studies. The meta-analysis was carried out using the activation likelihood estimation (ALE) method.
Results: We identified several distinct regions in the cerebellum involved in fear learning, including culmen (volume= 696mm3; ALEeValue(10x-3)=19.2), lobules IV-VI (volumes=696 and 288 mm3; ALE-Value(10x-3)=15.6 and 15.0), and cerebellar tonsils (volumes=336, 168, and 120mm3; ALE-Value(10x-3)=15.0, 13.0, 11.9).
Conclusions: These regions have been implicated in fear acquisition, consolidation of fear memories and expression of conditioned fear responses. As the cerebellum is thought to play a role in other types of associative learning mechanisms as well, it is hypothesized that it has a general role in prediction and timing. Our meta-analysis highlights the potential role of the cerebellum in human cognition and emotion. Future studies are needed to further clarify the mechanistic role of the cerebellum in higher order functions and neuropsychiatric disorders.

Keywords: fear learning, cerebellum, fMRI, meta-analysis

261. Resting-State Intrinsic Network Connectivity: Associations with Posttraumatic Stress Disorder Symptom Clusters

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Background: The influence of large-scale intrinsic connectivity networks (ICNs) within the human brain has been increasingly recognized as essential to the understanding of higher cognitive function, with particular emphasis on the central executive, salience (SN), and default mode (DMN) networks. The objective of this study was to understand patterns of network connectivity that significantly correlate with PTSD symptomatology.
Methods: PTSD patients (N=21) underwent resting-state fMRI scans. Independent component analyses were used to isolate 20 spatiotemporally independent components, which were spatially correlated with existing ICN masks. Multivariate analyses of covariance were used to determine independent correlations of PTSD symptom clusters with connectivity patterns within and between components.
Results: Increased hyperarousal was associated with decreased connectivity of the left ventral anterior insula and superior temporal gyrus within the SN. In contrast, depersonalization/derealization symptom severity was negatively associated with connectivity of right perigenual anterior cingulate cortex and ventromedial prefrontal cortex within the DMN. Altered synchrony between ventral anterior and posterior DMN components was also associated with heightened depersonalization/derealization.
Conclusions: These findings provide evidence for distinct ICN alterations underlying symptoms of hyperarousal and depersonalization/derealization, the latter often associated with hypoarousal, and increases our understanding of the neurobiological correlates of PTSD and its dissociative subtype.

Keywords: Posttraumatic Stress Disorder, Functional Neuroimaging, Intrinsic Connectivity Networks
Supported by: Lawson Health Research Institute

262. Acute Changes in Regional Cerebral Blood Flow After Deep Brain Stimulation in Patients with Obsessive-Compulsive Disorder

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Background: Deep brain stimulation (DBS) is a reversible, non-lesion based treatment for those with intractable obsessive-compulsive disorder (OCD). The first studies of DBS for OCD stimulating the ventral capsule/ventral striatum (VC/VS) yielded encouraging results for this neuroanatomical site's therapeutic efficacy. This investigation was conducted to better understand which regions of the cortico-striatal-thalamic-cortical network may play a central role in the effectiveness of VC/VS DBS for OCD.
Methods: Six patients receiving DBS of the VC/VS for OCD underwent oxygen-15 positron emission tomography (O-15 PET) scanning. Monopolar DBS was delivered at each of the four different electrodes on the stimulating lead in the VC/VS. The data were analyzed using SPM5. Paired t-tests were run in SPSS to identify significant changes in regional cerebral blood flow (rCBF) between stimulation conditions. Pearson's r correlations were run between these significant changes in rCBF and changes in OCD and depressive symptom severity.
Results: Perfusion in the dorsal anterior cingulate cortex (dACC) significantly increased when monopolar DBS was turned on at the most ventral DBS contact, and this increased dACC activity was correlated with reductions in depressive symptom severity [$r(5) = -0.994$, $p = 0.001$]. Perfusion in the thalamus, striatum, and pallidum significantly increased when DBS was turned on at the most dorsal contact.
Conclusions: DBS of the VC/VS appears to modulate activity in regions implicated in the pathophysiology of OCD. We found evidence that DBS at the most ventral site was associated with clinical changes in depressive symptom severity, but not in OCD symptom severity.

Keywords: Positron Emission Tomography, Obsessive-Compulsive Disorder, Deep Brain Stimulation, Neuromodulation, Cortico-Striatal-Thalamic-Cortical Circuit
Supported by: R01MH073111

263. A Smaller Amygdala Is Associated With Anxiety in Parkinson's Disease: A Combined Freesurfer – Voxel-based Morphometry Study

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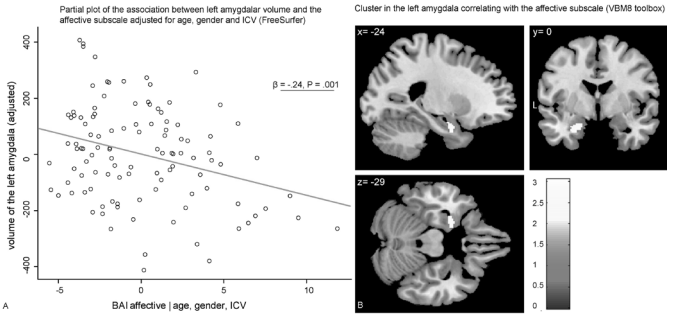
Background: Up to 50 percent of Parkinson's disease (PD) patients develop symptoms of anxiety during the course of their illness, a percentage that is much higher than in the general population, suggesting that pathological alterations associated with PD partly underlie these symptoms. So far only a limited amount of studies has been conducted on the neural correlates of anxiety in PD.
Methods: We performed a cross-sectional study in 110 early-stage PD patients (age: 64.6±10.3 years) to investigate the association between anxiety symptoms and volume of the hippocampus and amygdala. We used both FreeSurfer and voxel-based morphometry (VBM) for the volumetric analyses.
Results: Both the FreeSurfer (β = -0.24, P=.001) and VBM (r = -0.23, P=.016) analyses showed a negative correlation between the severity of anxiety symptoms (measured with the Beck Anxiety Inventory) and volume of the left amygdala. This association was independent of the severity of motor symptoms, autonomic dysfunction and medication status and was predominantly driven by the psychological symptoms of anxiety.
Conclusions: These results confirm previous studies in the general population showing lower left amygdalar volume in anxious patients. Whether this volume decrease constitutes a premorbid trait, a Parkinson-associated neurobiological susceptibility to anxiety or the consequence of chronic anxiety symptoms remains to be determined by future prospective longitudinal studies. Nonetheless, we tentatively hypothesize that the Parkinson pathology is responsible for the volume loss of the amygdala and the concomitant development of anxiety symptoms.



Keywords: anxiety, amygdala, Parkinson, MRI, structure

264. Conflict Learning Curve and Neural Activity in Individuals at High and Low Risk for Depression

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Background: This study was to investigate the learning curve of performing a Simon task and the underlying neural systems in persons at high and low risk for depression.
Methods: A functional magnetic resonance imaging (fMRI) study was performed on 143 participants, 83 of which had a high familial risk to develop major depression (33.12±12.69 years old, 37 males, 46 females), 60 participants with a low familial risk to develop major depression (26.72±13.22 years old, 26 males, 34 females). We acquired 10 runs of functional images from each participant during the performance of a standard simon task. The performance was assessed using reaction time (RT) that was used to fit a nonlinear mixed-effect model with an exponential decay function. We used the curve fittings to model the fMRI data. We then compared the neural activity governing the learning curve between the risk groups using Bayesian posterior inference at posterior probability threshold greater than 98.75%.
Results: The task-related neural activity changed following an exponential decay rule, given by the type of equation Y = b1-b2/(1+exp(-(t-b3)/b4)) where b1, b2, b3 and b4 were the learning model parameters. By comparing the activity between the high and low familial risk for depression, we found that the neural activity governing the learning process was significantly lower in high risk group than low risk group within the left and right caudate neclei.
Conclusions: The learning process is governed by a logistic-like exponential decay function. The persons who are at high risk for developing depression have abnormal neural activity in caudate nucleus that has been known to control a learning process.

Keywords: Depression, fMRI, Stroop and Simon task, Conflict Leaning, Nonlinear Mixed-effect Model
Supported by: NIMH 36197

265. Aberrant Fronto-Striatal and Fronto-Limbic Functional Connectivity in Youth with Tourette's Syndrome

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Background: Task-based fMRI findings suggest that the abnormal functioning of fronto-striatal circuits likely underlies the poor control over tic behaviors in Tourette's Syndrome (TS). Other data suggest that limbic areas are involved in TS pathophysiology. In this present study, we assessed resting state functional connectivity within fronto-striatal and fronto-limbic circuits in youth with TS.
Methods: This study included 16 children and adolescents with TS (11.44 + 2.5 years) and 16 matched, healthy controls (11.44 + 2.3 years). We collected resting state fMRI data and used limbic (L. and R. amygdala and hippocampus) and striatal (L. and R. caudate and

putamen) seed regions in functional connectivity analyses. We also explored the effects of comorbid OCD and ADHD on fronto-striatal and fronto-limbic connectivity in TS.
Results: In the TS compared to control groups, we detected significantly less functional connectivity between bilateral caudate and left precentral gyrus (-34 -4 62), and greater connectivity between bilateral hippocampus and bilateral precentral gyri (L: -46 4 40 and R: 62 6 36). These group differences remained after controlling for the presence of comorbid OCD and comorbid OCD and ADHD together, but not after controlling for ADHD alone.
Conclusions: These preliminary findings point to abnormalities in the functional connectivity of both fronto-striatal and fronto-limbic circuits in children and adolescents with TS. The presence of comorbid OCD, but not ADHD, seemed to contribute to these findings of decreased fronto-striatal and increased fronto-limbic connectivity in TS youth.

Keywords: Tourette's, functional magnetic resonance imaging, functional connectivity, resting state, youth

266. The Functional Brain Characteristics of Developmental Stuttering

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Background: Stuttering follows a developmental trajectory similar to that of many other child-onset developmental disorders. In this study we examined the common and unique neural networks involved in the pathogenesis of stuttering.
Methods: MRI data were collected from 31 persons with stuttering (PWS) and 31 age- and sex- matched fluent controls (HCs), while participants were instructed to rest with eyes closed in scanner, remain still, but not to fall asleep. One PWS and 2 HCs were excluded from further analysis due to excessive head motion measured by mean framewise displacement.
Results: Increased regional amplitude and homogeneity were present in the perisylvian language networks of PWS. The left Heschl's and insular gyri were the brain structures where altered amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), and degree centrality (DC) converged. Connectivity analyses based on the overlap of ALFF, ReHo, and DC suggested that these regions with altered baseline activity became increasingly coupled to adjacent perisylvian components. Findings were unchanged when controlling for head motion, use of medications, and comorbid psychiatric illnesses among PWS.
Conclusions: Our prior studies have demonstrated altered brain activation in PWS while performing the Simon Spatial Incompatibility Task. Stuttering is characterized by blunted activation in the left dorsolateral prefrontal cortex during context-dependent adaptation as well as hyper-activation in multiple frontostriatal regions during conflict resolution. Providing complimentary information, current resting-state analyses have identified distinctive feature of brain functioning in PWS, as evidenced by anomalies of baseline brain activity specifically, in perisylvian language regions.

Keywords: Magnetic resonance imaging, Speech, Stuttering, Resting-state fMRI, Development
Supported by: This work is supported by the McGue Millhiser Family Trust and the Suzanne Crosby Murphy Endowment at Columbia University

267. Associations of IQ Discrepancies with Brain Activation During Conflict Resolution

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Background: Verbal-Performance IQ (VIQ-PIQ) discrepancies are common across childhood developmental disorders. For example, PIQ is typically greater than VIQ (PIQ>VIQ) in Autism, Dyslexia, and Language Disorder and VIQ>PIQ in children with Non-Verbal Learning Disability. In healthy individuals, this discrepancy is associated with significant cortical thinning (VIQ>PIQ) or thickening (PIQ>VIQ) in frontal portions of frontostriatal circuits (inferior frontal gyrus and anterior cingulate cortex). Herein, we assessed whether functional abnormalities in these circuits may also be associated with VIQ-PIQ discrepancies.
Methods: FMRI data was collected from 46 healthy individuals (7-22 years) during their performance of the Simon task. General linear modeling was used to assess the effects of VIQ-PIQ discrepancies on frontostriatal activations during correct responses to conflict stimuli.
Results: Activation during conflict trials was positively associated with age and inversely associated with the magnitude of the VIQ-PIQ discrepancy in frontostriatal regions, while controlling for age and sex.
Conclusions: Greater conflict-related frontostriatal activation with advancing age reflects the typical functional development of these circuits. These findings of decreased activation with greater IQ discrepancies suggest that functional abnormalities in these circuits may contribute to discrepancies between (or deficits in) specific cognitive abilities in healthy individuals. We now plan to use these methods to assess associations of these discrepancies with frontostriatal structure and function across various psychiatric disorders in which specific cognitive abilities are impaired.

Keywords: IQ Discrepancies, Conflict Resolution, FMRI
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268. Shared Cerebellar Phenotypes in Autism Spectrum Disorders and Schizophrenia

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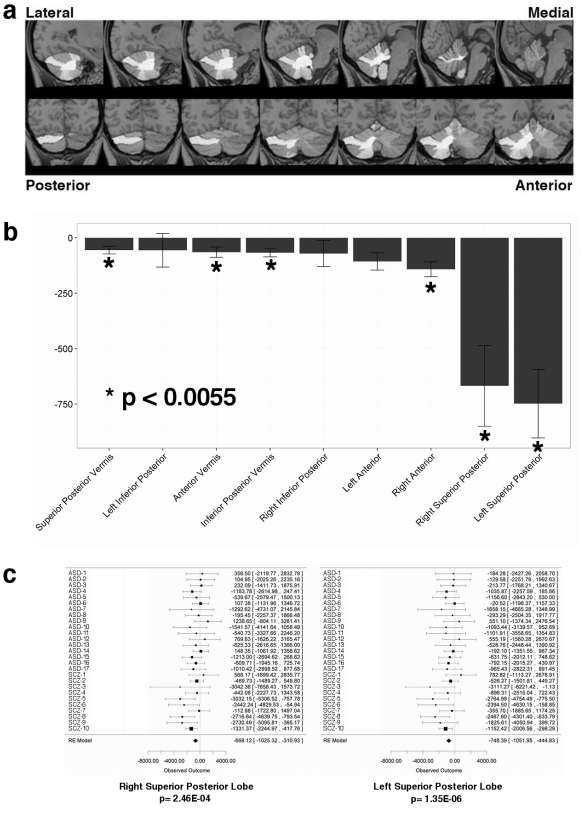
Background: The cerebellum has been implicated as a potential mediator of pathophysiology in psychiatric disorders, concurrent with converging evidence of its role in higher-order cognitive functions. Here, we examined the extent of cerebellar involvement as shared biomarkers across disorders, indicating its role in mediating specific cognitive functions while these functions may be coincident with the common underlying deficit across disorders examined.

Methods: Structural brain scans from 27 samples (510 controls/466 ASD, and 317 controls/313 schizophrenia; N= 1606) were processed using the MAGeT Brain algorithm for automated segmentation of the cerebellum (Figure a). Common effects of diagnosis on cerebellar volumes were examined using multiple linear regression accounting for age, sex, and intracranial volume as covariates separately per site. Effect sizes were then pooled using random effects meta-analysis.
Results: As expected, the strongest associations of diagnosis were found with those cerebellar subregions known to be involved in social cognition and executive function (Figure b, c; superior posterior lobes)--both common deficits across ASD and schizophrenia. Results additionally indicate altered motor function to a lesser extent (anterior lobes) and global cerebellar deficits (p=3.84E-05) (Figure b).
Conclusions: Results suggest common deficits in cerebellar development, which may contribute to shared deficits in symptom dimensions across ASD and schizophrenia. These findings indicate the possibility of mutual biological phenotypes, aiming towards examining symptom dimensionality within neuropsychiatric disorders which may shed novel insights into pathophysiology.



Keywords: Cerebellum, Autism, Schizophrenia, MRI
Supported by: W. Garfield Weston Foundation, Michael J. Fox Foundation, Alzheimer's Society, National Sciences and Engineering Research Council of Canada, Canadian Institutes of Health Research, and Brain Canada.

269. Amygdala and Hippocampal Morphology in Children with High Functioning Autism Spectrum Disorder

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Background: The amygdala and hippocampus are implicated in the neuropathology of autism spectrum disorder (ASD). Controversy exists, however, regarding the specific nature of these abnormalities in ASD. This study examines differences in amygdala and hippocampal morphology (shape and volume) between children with high functioning autism (HFA) and typically developing (TD) children.
Methods: High resolution T1 scans from 82 children with HFA or Asperger's Disorder (mean age = 10.5 years), along with 190 TD children (mean age =10.3) were examined. Children underwent standardized assessments for autism, psychopathology, and cognitive functioning. Amygdala and hippocampal regions were extracted using a validated segmentation pipeline consisting of two iterations of the multi-atlas likelihood fusion (MALF) algorithm, which incorporates anatomical features from multiple atlases with a variety of biological phenotypes. For each structure, large deformation diffeomorphic metric mapping (LDDMM) was used to transfer a common template surface onto a triangulated surface contouring the amygdala and hippocampus for each subject. Deformation maps were then computed.
Results: The right hippocampus was larger in children with HFA (p = 0.012) compared to TD children. When controlling for total cerebral volume, these group differences approached significance (p = 0.066). Shape analysis revealed local volume expansion in the right hippocampus in a region corresponding to the subiculum and CA1. No group differences in left hippocampal or amygdala volumes were present.
Conclusions: This is one of the first studies to reveal hippocampal volume and shape abnormalities in ASD. Findings will be discussed in relation to the pathophysiological and clinical manifestations of ASD.

Keywords: autism spectrum disorders, amygdala, hippocampal, morphology, children
Supported by: NIH: R01NS048527-08, UL1 TR 000424-06, P41 EB015909-13; Autism Speaks Foundation #2506

270. Altered Cortical Trajectories in Autism Spectrum Disorders: Relation to Symptomatology

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental condition that persists across life span affecting about 1 in 88 individuals. Several studies on brain size have shown brain overgrowth in early ages followed by arrested growth in later ages in ASD. Therefore, the study of trajectories of cortical growth in ASD can provide critical information that might help in understanding the etiology of ASD.

Methods: MRI scans of 580 male subjects consisting of typical controls (CTL) (n = 316, age = 17.0 ± 6.4 years) and people with ASD (n = 264, age = 17.2 ± 6.2 years) were processed using the CIVET pipeline and cortical thickness was obtained for each subject at 81,924 cortical points. Age-related growth trajectories were obtained using general linear model. Clusters of cortical points with significant difference between ASD and CTL in the trajectory of cortical growth were obtained. Lastly, Pearson correlation coefficients were used to compute relationships between regional cortical abnormalities and 3 domains of the Autism Diagnostic Observation Schedule (ADOS).
Results: Significant group difference was observed in several cortical regions in bilateral temporal, occipital, parietal and frontal cortices. Significant correlations between cortical thickness of right posterior temporal and right medial occipital-temporal clusters and ADOS Social and ADOS Communication were observed.
Conclusions: Altered cortical trajectories in ASD were observed in several cortical regions including bilateral temporal, right inferior frontal and right medial occipital cortices. Regional cortical abnormalities in right posterior temporal and right medial occipital-temporal clusters predicted two core behaviors associated with ASD, indicating the utility of investigating cortical growth trajectories in ASD.

Keywords: Autism spectrum disorders, Cortical trajectories, Neuroimaging, Symptom severity, Behavior
Supported by: The Azrieli Neurodevelopmental Research Program in partnership with Brain Canada Multi-Investigator Research Initiative (MIRI) grant

271. Dopamine Transporter Gene Variation Modulates Intrinsic Brain Activity in Children with Attention-Deficit Hyperactivity Disorder

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Background: The dopamine transporter gene (*DAT1*) has been consistently reported to be associated with attention-deficit hyperactivity disorder (ADHD). However, studies have not characterized the resting brain alterations in children with ADHD and their correlations with the severity of ADHD symptoms. This study aimed to examine the relationship between *DAT1* genotype and resting state functional connectivity in children with ADHD.
Methods: Using resting state functional MRI (RS-fMRI) and genetic analysis of the *DAT1* gene, we investigated how intrinsic brain activity contributed to ADHD depending on *DAT1* genotype in 37 drug-naïve children with ADHD, including 17 subjects with a haplotype of rs27048 (C)/rs429699 (T) and 20 subjects without this C/T haplotype. We analyzed intrinsic functional brain architecture with the fractional amplitude of low-frequency fluctuations (fALFFs).
Results: We found an association of ADHD with distinct intrinsic brain activity pattern depending on *DAT1* haplotype. A haplotype of rs27048 (C)/rs429699 (T) was associated with fALFF decrease in the left superior temporal gyrus, left cingulate gyrus, and left precentral/postcentral gyri. The severity of ADHD symptom was negatively correlated with fALFF in bilateral middle and inferior occipital gyri. These results remained statistically significant after corrections for multiple comparisons.
Conclusions: A novel gene-brain-behavior association was identified in which intrinsic activity alternations in distinct brain regions measured by fALFF was related to *DAT1* haplotype and ADHD symptoms in children with ADHD. Our findings could be a key to better understanding the pathway from genotype to phenotype in ADHD.

Keywords: imaging genetics, attention deficit hyperactivity disorder, dopamine transporter gene
Supported by: NSC96-2628-B-002-069-MY3

272. Brain Structure and ADHD Across the Life Span: An Enigma Collaboration

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Background: Neuroimaging studies show structural alterations of various brain regions in children and adults diagnosed with ADHD. In part due to inconsistencies in published results, it remains unclear, however, how these differences develop across the lifespan, and whether effects are brain-wide or localized to particular neurological structures and pathways. To clarify brain changes across the lifespan in a large worldwide sample, an ADHD Working Group was formed within the ENIGMA consortium (http://enigma.ini.usc.edu/).
Methods: Within the ENIGMA-ADHD Working Group cohorts from around the world analyzed MRI scans using fully automated and validated neuroimaging segmentation software (FSL FIRST or FreeSurfer), for which protocols are available on our website. Volumetric summaries of subcortical regions were pooled together and shared across the consortium. Meta- and Mega-analysis for the case-control volume differences of hippocampus, nucleus accumbens, amygdala, caudate nucleus, putamen, pallidum, and thalamus were carried out.
Results: The working group comprises 23 international sites including 1544 cases and 1729 controls. This pooled sample has an age-range of 4-63 years and includes 66% males. Our preliminary case-control meta-analysis showed subtle but significantly smaller volumes for the nucleus accumbens (Cohen's *d*: 0.13), amygdala (*d*: 0.15), caudate nucleus (*d*: 0.11), and putamen (*d*: 0.11) for cases compared to controls. The results of the mega-analysis showed similar effect sizes, with greater significance (lower p-value). Several structures had age-dependent effects.
Conclusions: Brain structure differences related to ADHD across the lifespan remain largely unexplored. As large, well-powered longitudinal studies are still scarce, the ENIGMA-ADHD Working Group, with a large cross-sectional sample across six decades of the lifespan, is beginning to address this gap.

Keywords: ADHD, imaging, meta-analysis, subcortical volumes
Supported by: U544EB020403 and NWO:016-130-669).

273. Altered Striatal Resting-State Connectivity to Sensory and Language Processing Cortical Areas in Autism

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Background: Resting-state connectivity studies in school-age children with autism spectrum disorder (ASD) have shown increased connectivity between striatum (caudate/putamen) and associative/limbic cortex. We hypothesized that there may be similar striatal hyperconnectivity in adolescent males with ASD.
Methods: We studied 7 males (Age 13-17) with ASD and 10 age-matched typically developing (TD) males. MRI imaging at 3T included a 6-minute resting-state fMRI scan. Resting state analysis included motion correction, intensity normalization and band-pass temporal filtering (0.05-0.001 Hz), regression of nuisance covariates. We used seed regions in the bilateral caudate and putamen to generate the correlation of the time signal with 55 ipsilateral cortical and subcortical regions.
Results: In ASD compared to TD group, a number of regions demonstrated significant differences (uncorrected $p < 0.05$) in their intrahemispheric resting state correlation with caudate and/or putamen. There were no significant differences in correlations between caudate/putamen and associative/limbic areas implicated in previous study of school-age children. ASD group had decreased connectivity between striatum and auditory and language processing areas(Heschl's gyrus and planum polare) and somatosensory processing areas(parietal operculum), and increased connectivity between striatum and visual processing areas (occipital cortex and superior parietal lobule).
Conclusions: This preliminary study suggests that striatal connectivity to sensory processing regions may be altered in adolescents with ASD, with hyperconnectivity to visual processing regions and hypoconnectivity to auditory and somatosensory processing regions. Further studies to determine whether these alterations are related to sensory processing and language abnormalities in ASD are needed.

The R-squared and p-value for the linear model of average connectivity between regions by group

Seed Region	Read Region	r^2	p-value	Group Difference
R Caudate	R Planum Polare	0.425	0.005	ASD<TD
R Caudate	R Parietal Operculum	0.411	0.006	ASD<TD
R Caudate	R Heschl's Gyrus	0.248	0.042	ASD<TD
L Caudate	L Parietal Operculum	0.313	0.020	ASD<TD
L Caudate	L Lateral Occipital (inf)	0.260	0.037	ASD>TD
R Putamen	R Superior Parietal Lobule	0.334	0.015	ASD>TD
R Putamen	R Pallidum	0.292	0.025	ASD>TD
L Putamen	L Thalamus	0.286	0.027	ASD>TD
L Putamen	L Middle Frontal Gyrus	0.281	0.029	ASD<TD

Keywords: autism, resting state fMRI, neuroimaging, striatum, functional connectivity
Supported by: APIRE Fellowship; AACAP Pilot Award; NIH/NICHD 5P30 HD004147-39

274. Multivariate Regression Analysis of Change in Symptom Dimensions and Neural Activity in Behaviorally and Emotionally Dysregulated Youth

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Background: The ways in which neural function during emotion processing changes in synchrony with symptom changes in youth will aid in our understanding of neural mechanisms of pediatric psychiatric disorders. We examined relationships among longitudinal changes in amygdala-prefrontal cortical neural circuitry functioning and symptom changes during emotion processing in youth from the Longitudinal Assessment of Manic Symptoms (LAMS) Study.
Methods: Fifty-eight LAMS youth [age=10.29-19.27(mean=14.50(s.d.=1.78))] completed a dynamic emotional face processing task at two time points 13-31 months apart(mean=21.76(s.d.=4.15)). Multivariate regression analysis was used to predict changes in the dimensional measures K-SAD Mania Rating Scale (KMRS), K-SAD Depression Rating Scale (KDRS), Screen for Child Anxiety Related Disorders (SCARED), behavioral and emotional dysregulation, measured by the Parental General Behavior Inventory-10 item(PGBI-10M) from changes in neural activity and functional connectivity during the emotion processing task, specifically for all emotional faces versus control (shape) baseline. We accounted for medication, age, IQ, gender, and site.
Results: Increased positive amygdala-anterior cingulate cortex (ACC) connectivity between scan1 and scan2, and having a bipolar spectrum disorder (BPSD) diagnosis at scan1 predicted improvement in PGBI-10M score between scan1 and scan2 [p=0.016(eta2=0.111) and p=0.014(eta2=0.115), respectively], while having a disruptive behavior disorder diagnosis at scan1 predicted improvement in depression (KDRS) symptom severity between scan1 and scan2 [p=0.011(eta2=0.112)].
Conclusions: Together, these findings indicate that during emotion processing, increased functional connectivity between amygdala and a key prefrontal cortical region implicated in emotional regulation, the ACC, is associated with improvement in behavioral and emotional regulation in youth, and may be an important neural marker to guide interventions.

Keywords: fMRI, Adolescent, Amygdala, ACC, Emotion
Supported by: RO1MH073953

275. Altered Resting State Connectivity in Behaviorally and Emotionally Dysregulated Youth in the Longitudinal Assessment of Manic Symptoms (LAMS) Study

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Background: The Research Domain Criteria (RDoC) advocates using a dimensional research approach to study transdiagnostic pathophysiological processes in psychiatric disorders. Studying brain-behavior relationships using neuroimaging techniques, such as resting state functional connectivity (RSC), is ideally suited to follow the RDoC framework.
Methods: Following the RDoC dimensional research approach, we examined relationships between RSC and symptom dimensions (dimensional severity measures of behavioral and emotional dysregulation [PGBI-10M], mania [K-MRS], depression [K-DRS], anxiety [SCARED]) and diagnostic categories (Bipolar Spectrum Disorders, Attention Deficit Hyperactivity Disorder, Anxiety Disorders, Disruptive Behavior Disorders) in behaviorally and emotionally dysregulated youth in the Longitudinal Assessment of Manic Symptoms (LAMS) study (n=42). RSC analyses examined functional coupling between an amygdala seed region and a priori regions of interest: prefrontal cortex (BA10, BA11, BA24/32, BA47), striatum (caudate head and body, putamen, and ventral striatum), and insula.
Results: Regardless of diagnosis and after accounting for demographic variables, RSC showed significant negative relationships with two symptom dimensions across all LAMS youth ($p<.05$ voxelwise, $p<.05$ corrected): 1) PGBI-10M and the amygdala-left posterior insula/bilateral putamen RSC; and 2) K-DRS and amygdala-right posterior insula RSC. There were no significant relationships between diagnostic categories and resting state connectivity.
Conclusions: Decreased amygdala-posterior insula RSC was significantly associated with increased severity of symptom dimensions across all LAMS youth, regardless of diagnosis, suggesting intrinsic functional uncoupling of key neural circuitry involved in emotion processing and regulation. Our findings add to the growing body of literature in support of the RDoC dimensional research approach to the transdiagnostic study of psychiatric disorders.

Keywords: RDoC, Resting State, fMRI, emotion, amygdala
Supported by: 2R01 MH73953-06A1; 2R01 MH73816-06A1; 2R01 MH73967-06A1; 2R01 MH73801-06A1

276. Paradoxical Recruitment of Fear Circuitry to Emotional Faces in Pediatric Post-traumatic Stress Disorder

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Background: Adult PTSD is associated with abnormal fear circuit function, including increased amygdala and dorsal anterior cingulate (dACC), and decreased ventromedial prefrontal cortex (vmPFC) recruitment. However, few studies have examined fear circuit function in pediatric PTSD, including age-related change and functional connectivity.
Methods: Twenty-five youth with PTSD and 28 healthy youth completed a dynamic emotional faces task during fMRI. Participants identified a color overlying morphing emotional faces (neutral to angry or happy) or shape. Functional activation was examined, followed by psychophysiological interaction analyses using activation clusters as seeds. Group and age-related differences were examined in *a priori* regions (amygdala/hippocampus, mPFC) with multiple comparison correction.
Results: PTSD youth showed dorsomedial (dm)PFC (BA 9) hyperactivation. Group by age interactions in the amygdala and rostral (r)ACC (BA 32) showed negative and positive correlations with age in healthy and PTSD youth, respectively. A group by condition interaction in the dACC (BA 24/32) showed no group differences to angry faces, but hyperactivation to happy faces in PTSD youth. Connectivity analyses revealed multiple group by condition interactions including dACC-insula and –dmPFC, and dmPFC-amygdala, -hippocampus, and -insula. In each case, PTSD youth showed hypoconnectivity to angry faces, but hyperconnectivity to happy faces. Abnormal function and connectivity patterns were further associated with PTSD symptoms and illness duration.
Conclusions: Pediatric PTSD is characterized by emotion-specific and age-related abnormalities in circuitry underlying threat appraisal and fear regulation. Paradoxical neural responses to happy and angry faces may indicate abnormalities in threat-safety discrimination of emotional faces, which may differ from adult PTSD.

Keywords: pediatric PTSD, amygdala, prefrontal cortex, fMRI
Supported by: K08 MH100267; NARSAD Young Investigator Grant; AACAP Junior Investigator Award; UW ICTR Translational Research Pilot Grant Award

277. Evidence of Altered Neuropil Development in ADHD Children: A Longitudinal *In Vivo* ³¹P MRS Study at 3 Tesla

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Background: *In vivo* ^{31}P MRS is sensitive in detecting changes during development in the molecular biochemistry of cortex that reflects neuropil expansion/contraction by measuring precursors of membrane phospholipids (MPLs) [phosphocholine (PC); phoshoethanolamine (PE)]. In a cross-sectional study, we have reported subcortical/cortical deficits in MPL precursor levels of ADHD children that are suggestive of altered neuropil development (Stanley et al. 2008). In this study, the purpose was to investigate whether longitudinal changes in precursor levels differed between ADHD and controls.

Methods: A 3D multi-voxel ^{31}P MRS at 3T was collected in 31 ADHD males (10.7±2.4yrs) and 31 controls (10.2±2.32yrs) at baseline, and at 1- and 2-year follow-up. Metabolite levels from the DLPFC, ACC, striatum and thalamus were quantified, and group differences at baseline and group-by-time-point interactions were statistically analyzed.

Results: At baseline, PC levels were reduced in the right DLPFC (p=0.020) and right ACC (p=0.042) of ADHD children compared to controls. The longitudinal data showed decreasing PE levels with age in the right DLPFC (p=0.021), decreasing PC levels with age in the left striatum (p=0.0049), and increasing PE levels with age in the right thalamus (p=0.032) all in ADHD children compared to controls.

Conclusions: These results show, for the first time distinct altered developmental trajectories of MPL precursor levels in the DLPFC, striatum and thalamus of ADHD children. Active MPL synthesis is critical in providing cell membrane structure to dendritic and synaptic connections and astrocytes (i.e., neuropil expansion) and these deficits continue to support a greater rate of neuropil contraction over time in the DLPFC and striatum of ADHD children.

Table 1. Associations of ULK4 genetic variants with risk fo autism and gene expression in prefrontal cortex in human postmortem brain.

SNP	BP	Nearby Gene	A1	A2	T	U	OR	Ptdt	Pexpr	Splicing	nsSNP	Polyphen	RegPotential	Conservation
rs4973978	41642549	ULK4	C	A	45	27	1.667	0.03389	2.71E-01	–	–	–	0	0.008
rs9824775	41645175	ULK4	G	A	36	24	1.5	0.1213	3.45E-01	–	–	–	0	0.001
rs6783612	41649598	ULK4	A	G	76	62	1.226	0.2334	7.72E-01	–	–	–	0	0
rs9852303	41734529	ULK4	A	G	96	59	1.627	0.00296	3.33E-06	–	–	–	0	0.004
rs6599175	41761013	ULK4	G	A	96	59	1.627	0.00296	3.98E-06	–	–	–	NA	0
rs4973893	41811474	ULK4	A	G	71	103	0.6893	0.01527	2.56E-01	–	–	–	0	0
rs900569	41834977	ULK4	A	G	163	133	1.226	0.08121	6.88E-04	–	–	–	0	0.001
rs1716670	41885575	ULK4	A	G	75	104	0.7212	0.03019	5.76E-02	Y	–	–	NA	0
rs1052501	41900402	ULK4	G	A	96	58	1.655	0.00220	1.77E-08	Y	Y	benign	0.095	0.971
rs1716975	41935010	ULK4	A	G	98	56	1.75	0.00071	4.94E-07	Y	Y	benign	0.077	0.066
rs2272007	41971140	ULK4	A	G	98	58	1.69	0.00136	4.94E-07	Y	Y	benign	0.016	1
rs12635286	42026840	ULK4|TRAK1	G	A	96	57	1.684	0.00162	2.00E-03	–	–	–	0	0
rs17066958	42048961	ULK4|TRAK1	A	G	110	62	1.774	0.00025	3.04E-02	–	–	–	0	0
rs904269	42051626	ULK4|TRAK1	A	C	151	117	1.291	0.03781	7.22E-01	–	–	–	0	0.008
rs9847688	42054115	ULK4|TRAK1	C	A	113	69	1.638	0.00111	7.05E-02	–	–	–	0	0
rs9862024	42071245	ULK4|TRAK1	A	G	29	25	1.16	0.5862	5.66E-01	–	–	–	0	0

Figure 1. Genome browser of the ULK4 region

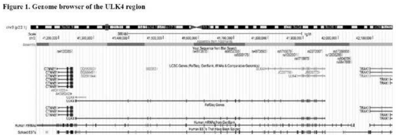
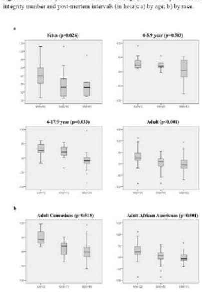


Figure 2 The cis-acting regulatory associations of autism-associated rs1716975 polymorphism in postnatal human brains. Analyses were based on general linear regression models adjusted for covariates of sex, age (at brain sample collection), RNA integrity number and post-mortem intervals (in hour): a) by age; b) by race.



Keywords: ADHD, longitudinal, MRS, membrane phospholipid metabolism, development

Supported by: R01MH065420; Lycaki-Young Funds from the State of Michigan

278. Hippocampal Glutamate and Obesity: A Translational Human and Animal Study

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Background: The hippocampus plays a critical role in food consumption. However, how the hippocampus is affected by obesity is not well understood. Here, we investigated the influence of body mass on hippocampal glutamate in high- and healthy-BMI humans and in an animal model of obesity.

Methods: Short echo proton spectroscopy data were analyzed from 35 participants (20 female; age 7-24 years) with a high BMI, and 25 normal-weight controls (15 female; age 7-24). A group of Long-Evans rats (P60-80) were split into three groups: (1) chow, (2) cafeteria diet + chow with extended access (23 hour/day), and (3) cafeteria diet + chow with restricted access (1 hour/day cafeteria diet, chow 23 hours). Animals were fed this diet for 40 days. Hippocampal slices were obtained from these rats. We recorded miniature excitatory postsynaptic currents (mEPSC) to determine if diet and/or obesity modified glutamatergic synaptic transmission in CA1 hippocampal neurons.

Results: In the right hippocampus, BMI was associated with glutamate concentration ($r = 0.37$, $p < 0.05$). When comparing high and healthy BMI groups, the high BMI group demonstrated greater right hippocampal glutamate concentration ($p < 0.05$). In rats with extended access to a cafeteria diet, hippocampal mean mEPSC frequency ($p < 0.05$) and amplitude ($p < 0.05$) was enhanced compared to hippocampal neurons from restricted access or chow groups.

Conclusions: Our results provide translational evidence that high body mass is positively correlated with increased hippocampal glutamate activity. Future experiments will seek to characterize the neurobiological consequences of increased glutamate on hippocampal function.

Keywords: obesity, glutamate, animal model, brain imaging, hippocampus

Supported by: Hotchkiss Brain Institute (HBI) Department of Clinical Neurosciences (DCNS) Pilot Fund

279. Neuroanatomical Signatures of Anorexia Nervosa: A Machine Learning Approach

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Background: The neurobiological underpinnings of AN are currently still incompletely understood, and there are currently no structural MRI biomarkers available to make inferences at an individual level. We present the results of a multivariate machine learning (ML) approach utilizing structural neuroanatomical scan data to differentiate AN patients from matched healthy controls at an individual subject level.

Methods: T1-weighted structural scans were acquired from 15 female patients with AN (age=20±4 years) and 15 demographically matched female controls (age=22±3 years). The least absolute shrinkage and selection operator (LASSO) algorithm was 'trained' using gray-matter and white matter volumes to predict individual subjects' diagnostic label. LASSO was 'trained' and 'tested' using a leave-one-out cross-validation approach.
Results: 25 of the 30 subjects were correctly classified translating into 86.7% sensitivity, 80.0% specificity and 83.3% accuracy and significant at p<0.001. Multiple neuroanatomical regions were relevant in distinguishing AN patients and healthy controls. The model probabilities – which quantify the likelihood of a subject of belonging to the patient group – were found to show correlations with Drive for Thinness clinical scores.
Conclusions: The proposed model reliably identifies a neuroanatomical signature of drive to thinness. The relevance of the probabilistic outcome of the model to course of illness, response to treatments and outcomes should be further investigated.

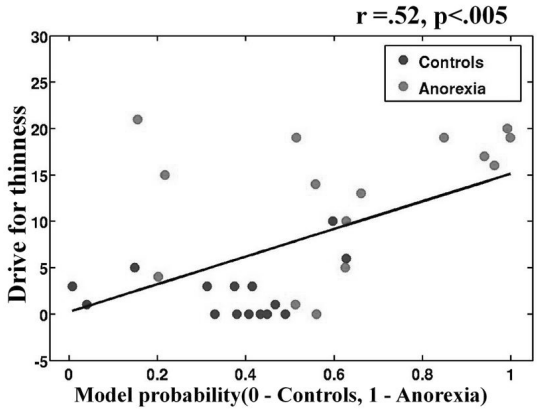

Figure 1. The scatterplot shows the relationship between model probability and EDI-II drive for thinness scores for patients with anorexia and controls.

Keywords: Anorexia Nervosa, NEUROANATOMY, Machine Learning, Eating Disorders, Imaging

280. Analyses of White Matter Integrity in Adolescents and Adults with Bulimia Nervosa

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Background: Our previous data point to structural and functional abnormalities in frontostriatal circuits in adolescents and adults with Bulimia Nervosa (BN). In this study we investigated white matter microstructure within these circuits in the same young women with BN.
Methods: Diffusion tensor imaging (DTI) data were acquired from 28 adolescents and adults with BN and 28 matched healthy control (HC) participants. Tract-Based Spatial Statistics (TBSS) was used to detect group differences in white matter integrity.
Results: Significant reductions in fractional anisotropy (FA) were detected in the BN compared to HC participants in the forceps minor, and superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFO), anterior thalamic radiation (ATR), and corticospinal tract (CST) of the left hemisphere. In the BN group, these FA reductions correlated positively with age while increases in radial diffusivity (RD) detected in the same tracts correlated inversely with age, after controlling for illness duration. In contrast, age correlated inversely with FA and positively with RD in these tracts in the HC group. FA reductions in forceps minor and major, left ATR and IFO correlated inversely with symptom severity and Stroop interference in the BN group.
Conclusions: These findings suggest that white matter integrity is reduced in BN in tracts extending through frontal and temporoparietal cortices. Group differences in age-related changes in both the integrity of these connections (FA) and myelination (RD) of these tracts in BN compared with healthy individuals may represent an abnormal trajectory of white matter development that contributes to the persistence of functional impairments in self-regulation in BN.

Keywords: Bulimia Nervosa, Eating Disorders, DTI, Fractional Anisotropy, Frontostriatal circuits
Supported by: NIMH grants K01-MH077652 and R01MH090062 (RM), the National Alliance for Research on Schizophrenia and Depression (NARSAD, RM and XH), and the Sackler Institute for Developmental Psychobiology, Columbia University.

281. Altered Neural Processing of Cognitive Control Among Offspring Exposed to Maternal Smoking in Utero

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Background: Despite substantial declines, 10-15% of US women smoke while pregnant today. Doing so impacts both maternal and fetal well-being, and is associated with a number of cognitive deficits that persist into adolescence. The causal mechanisms remain unclear. Examining neurobiological antecedents of cognitive and clinical outcomes may help to understand mechanisms and identify offspring at greatest risk. We here seek to identify alterations in cognitive-conflict related circuitry in offspring exposed in utero to maternal smoking.
Methods: 117 participants from a longitudinal 3-generation family study of depression were included. Pregnancy data were collected from the mother. Offspring were assessed directly over multiple waves spanning up to 30 years, using the age appropriate version of the SADS interview and behavioral/symptom self-reports. Participants were imaged on a 1.5T scanner while performing the Simon Spatial Incompatibility Task.
Results: Among exposed (n=28) as compared to either (i) age/gender matched (n=28) or (ii) all (n=89) unexposed, offspring, increased cognitive conflict was associated with bilateral reductions in anterior cingulate, orbitofrontal, insular, cuneus and precuneus, activity. Cingulate and oribitofrontal reductions were further associated with impulsivity and sensation-seeking (others behavioral and clinical measures will also be presented).
Conclusions: Patterns of reduced conflict-related activity are consistent with anatomical deficits and with greater rates of exter-

nalizing behaviors observed among exposed offspring, suggesting that prenatal tobacco exposure may impair circuits underlying behavioral regulation and thereby increase risk for later behavioral outcomes.

Keywords: prenatal smoking, functional imaging, simon task, impulsivity
Supported by: 1 K01DA029598; 5 R01 MH036197-28; NARSAD

282. N-Acetylcysteine Restores Impaired Amygdala-Insula Resting State Connectivity in Adolescents with Non-Suicidal Self-Injury

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Background: Non-suicidal self-injury (NSSI) is common in adolescents with few available treatments. N-acetylcysteine (NAC) has been tested in mood and habit disorders, and may have promise for treating NSSI in adolescents. Functional magnetic resonance imaging (fMRI) can be used to track brain changes within a clinical trial; resting-state functional connectivity (RSFC) can illuminate aberrant brain networks in adolescents with NSSI that could potentially be impacted by treatment.
Methods: Twenty-two female adolescent (13-21 years) with NSSI and 15 female healthy controls (similar ages) underwent baseline MRI scanning. Adolescents with NSSI were treated with open-labeled NAC for 8 weeks (1200mg/day weeks 1-2, 2400mg/day weeks 3-4, 3600mg/day weeks 5-8) and then repeated scanning. Repeated measures ANOVA tested change in number of NSSI behaviors per 2 weeks. We measured whole-brain amygdala RSFC in each participant; group-level analyses examined baseline differences between patients and controls and, within the NSSI group, pre-post NAC treatment changes in amygdala RSFC.
Results: At baseline, adolescents with NSSI demonstrated lower amygdala RSFC than controls in prefrontal cortex, insula, and posterior cingulate cortex ($z > 2.3$, $p < 0.05$, corrected). NAC treatment led to decreased NSSI behaviors ($F=3$, $p=0.036$). After treatment with NAC, the NSSI group showed an increase in amygdala-insular RSFC ($z > 2.3$, $p < 0.05$, corrected).
Conclusions: Impaired amygdala RSFC in adolescents with NSSI may underlie impaired emotion regulation associated with this behavior. Amygdala-insular interactions are important for interpreting the salience of external and internal stimuli and regulating emotional responses. NAC may be a promising treatment for NSSI in adolescents, perhaps via restoration of impaired amygdala-insular RSFC.

Keywords: non-suicidal self-injury, resting-state functional connectivity, n-acetylcysteine, amygdala, insula
Supported by: R21MH094558

283. Hippocampal Metabolite Laterality in Major Depressive Disorder

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Background: The hippocampus plays a determinant role in major depressive disorder (MDD) and alterations in hippocampal metabolites are reported in depressed youth and adults. However, these studies are limited by the use of large voxels and varied results. The goal of the present study was to examine the hippocampus using an angulated spectroscopic voxel, to better exclude extraneous brain regions.
Methods: 26 participants with MDD and 22 controls (26 females and 22 males, age 14-24) underwent a ^{1}H-MRS protocol consisting of a voxel directed to either the left or right hippocampus. Analysis was completed using the LCModel method, providing approximate maximum-likelihood estimates of metabolite concentrations and their uncertainties (Cramer-Rao lower bounds).
Results: MDD participants had lower NAA+NAAG concentrations in the left hippocampus ($p = 0.037$). Total Cr+PCr was also reduced ($p = 0.032$). In the right, increased inositol and Glx were found in the MDD group ($p= 0.001$; 0.008). Analysis using Spearmann correlations revealed a negative correlation of NAA+NAAG, and positive correlations of Glx and Ins with HamD scores.
Conclusions: Our findings of reduced NAA+NAAG and increased Glx and Ins are consistent with previous findings in MDD. Though not divided by functional output, the mammalian hippocampus is influenced by input-dependent asymmetry, whereby cortical input mitigates the number, density, and receptor characteristics of left-right hippocampal subregions. Our data may serve to more clearly define these functions, and their role in MDD severity. Taken together, modifications of the standard voxel placement has afforded more precise discrimination of the lateralized alterations in hippocampal biochemistry.

Keywords: major depressive disorder, NAA, hippocampus, spectroscopy, Glx
Supported by: Cuthbertson and Fischer Chair

284. Optimized Multielectrode tDCS Modulates Corticolimbic Networks: A Placebo-controlled Crossover Study

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Background: Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulatory technique using weak electrical

currents to alter cortical excitability. Currently, studies are exploring distinct stimulation parameters to optimize tDCS effects. Here, we aimed to test the differential effect of a novel, computationally-optimized multielectrode montage designed to improve targeting and efficiency of the induced electric field.
Methods: In a randomized, single-blind sham-controlled crossover study, 20 healthy subjects underwent three tDCS sessions (conventional, multielectrode and sham) using the Starstim system with 25 cm2 sponges and eight 3 cm2 Ag/AgCl Pi electrodes respectively, with two weeks of inter-session interval. Stimulation was applied for 20min targeting prefrontal regions. Resting state-fMRI scans were acquired immediately after tDCS sessions to identify functional tDCS-induced changes. We firstly examined the fractional amplitude of low-frequency fluctuations (fALFF) to determine between-condition differences on regional brain activity. Then, areas exhibiting fALFF differences were selected as regions-of-interest in a seed-based functional connectivity (FC) analysis within areas of the corticolimbic network.
Results: The multielectrode montage resulted in significantly higher fALFF values in frontopolar, middle and superior prefrontal cortices. Furthermore, an increase in FC between these regions and right hippocampus was specifically observed in this condition.
Conclusions: Optimized multielectrode tDCS induced a modulation on regional brain activity and FC in corticolimbic networks, thus suggesting this particular montage to be the adequate election when aiming to modulate brain activity in disorders involving corticolimbic network, which opens the possibility for new therapeutic approaches.

Keywords: tDCS, fMRI, corticolimbic, multielectrode, trail
Supported by: Carlos III Health Institute (PI12/01306)

285. Increased Insula Activity Is Associated with Improved Mood in Healthy Subjects on Clomipramine

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Background: Previous functional magnetic resonance imaging (fMRI) studies examined neural activity responses to emotional stimuli in healthy individuals after acute/subacute administration of antidepressants. We now report the neural effects of emotion induction stimuli on healthy subjects showing positive mood changes in response to repeated use of the antidepressant clomipramine.
Methods: Eighteen subjects with no personal or family history of psychiatric disorders participated in a 4-week open label trial of clomipramine. Evidence of treatment response was considered positive when subjects presented during a semi-structured interview with less irritability and tension in social interactions, improved decision making, higher self-confidence, and brighter mood. Neural response to fear-, happiness-, and anger-provoking pictures was explored using fMRI. All subjects were scanned at the end of the open label trail under the effect of clomipramine. Subjects with and without positive mood treatment changes were compared using independent t-test. Results were considered significant at $p<0.05$ corrected for multiple comparisons.
Results: The average dose of clomipramine was 37 mg/day and participants were 100% adherent. Thirty-three percent of the subjects had a positive mood treatment change. We found an increase in left insula activity in reaction to positive and negative emotion provoking stimuli in subjects with positive mood response, as compared to those without treatment response.
Conclusions: Prolonged use of low doses of the serotonin-norepinephrine reuptake inhibitor clomipramine can induce positive mood changes that are unrelated to psychopathology. Changes in insular activity during emotion induction modulated by clomipramine may be associated with improved perception of internal bodily states.

Keywords: clomipramine, fMRI, healthy volunteers, insula, emotion processing
Supported by: FAPESP: 01/00189-9

286. Intact Instrumental Learning from Reward and Punishment in Unmedicated Patients with Major Depressive Disorder

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Background: Reduced sensitivity to reward has been proposed as a key factor in major depressive disorder (MDD). Earlier studies reported dysfunction in neural circuits involved in reward and punishment processing, including ventral striatum (VS) and orbitofrontal cortex (OFC). Here we asked whether such dysfunction leads to impaired instrumental learning.
Methods: Model-based functional magnetic resonance imaging (fMRI) and an established instrumental learning task were used in 31 unmedicated patients with MDD and 31 controls. Reward and punishment learning was modeled with a standard Q-learning algorithm for trial-wise estimation of expected values and prediction errors (PE). These estimated parameters were used as parametric regressors for fMRI data analysis.
Results: There were no group differences in behavioral learning time courses or in estimated learning parameters (all $p>0.15$). fMRI showed robust main effects of expected value for reward in OFC and for punishment in anterior insula (all $p<0.05$, FWE-corrected). Similarly, strong main effects of reward PE were found in VS and OFC, and of punishment PE in anterior insula (all $p<0.05$, FWE-corrected). Importantly, even with highly sensitive region-of-interest analyses we found neither group differences for neural correlates of expected value or PE, nor correlations of fMRI responses with depressive symptom severity.
Conclusions: Using an established experimental paradigm and highly sensitive model-based analyses in a sufficiently powered sample, we found no behavioral or neural evidence for impaired instrumental learning in MDD. Our results question the notion of altered reward processing as a relevant mechanism and instead suggest intact instrumental learning in MDD, providing a basis for cognitive-behavioral treatment approaches.

Keywords: Major depressive disorder, fMRI, Instrumental learning, Reward, Computational modeling
Supported by: German Research Foundation

287. Omega-3 Fatty Acid Treatment Effect on Regional Brain Responses to a Stroop Task in Major Depression

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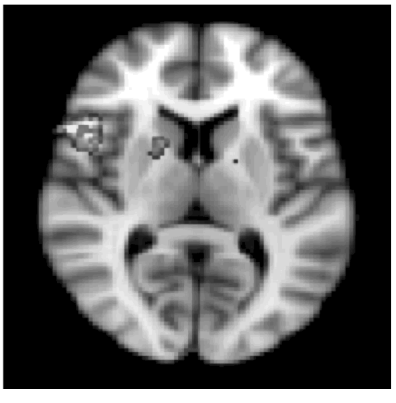
Background: Polyunsaturated fatty acids (PUFAs) are essential for brain function. Omega-3 PUFAs are low in major depression, and supplementation can have antidepressant effects. PUFA levels correlate with resting state regional brain glucose uptake; however, little is known about the impact of omega-3 PUFAs on brain activity during cognition, a functional domain adversely affected by depression.
Methods: Before and after 6-week omega-3 PUFA supplementation, patients with DSM-IV major depressive disorder (MDD) (n=16) and healthy volunteers (HV) (n=11) had plasma phospholipid levels of PUFAs measured, and performed a Stroop task during functional magnetic resonance 3T imaging (fMRI).
Results: In MDD, docosahexaenoic acid (DHA, 22:6n-3) levels after supplementation correlated with final Hamilton depression scores (R_2=0.27, p =0.04). During incongruent word-color blocs, there were no MDD-HV differences in error rates or reaction times at baseline, nor in baseline blood-oxygen-level dependent (BOLD) fMRI activity. However, decreases in interference-related activation were seen following PUFA treatment in both groups. DHA changes correlated negatively with regional changes in interference activation in HV (including superior frontal gyrus, thalamus, cerebellum, and superior parietal lobule) and positively in MDD (including inferior and middle frontal, and supramarginal gyri, caudate and putamen). **Figure:** DHA_{Time2} positive correlations with changes in BOLD activity, in MDD.
Conclusions: Omega-3 PUFA supplementation differentially affected BOLD brain activity in depressed and healthy volunteers. These findings indicate effects of PUFA supplementation on brain cognitive function in MDD and in healthy brain.



Keywords: PUFA, Depression, fMRI, Stroop
Supported by: NIH MH079033

288. Microstructural Abnormalities of White Matter Underlying Familial Risk for Depression

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Background: Tract-Based-Spatial-Statistics (TBSS) has shown microstructural abnormalities of white matter (WM) in persons at increased familial risk for developing major depressive disorder (MDD). Little is known about how familial risk status is correlated with the abnormalities of WM in people developing or not developing MDD.
Methods: The TBSS analysis was based on a 3-generation longitudinal study of offspring at high- or low-familial risk (HR, LR) for MDD by virtue of the presence of MDD in the proband generations. We stratified the 108 2nd and 3rd-generation offspring with usable DTI data by their familial risk and own depression status. We first examined the (1)29 depressed and 31 non-depressed individuals from HR families of depression, and (2)12 depressed and 36 nondepressed individuals from LR families. Subsequently, we examined the same individuals by MDD status, including (3)the 29 versus the 12 with MDD; and (4)the 31 versus the 36 without MDD.
Results: LR group: MDD-individuals had significantly decreased mean diffusivity (MD) values in frontal-gyri, brain-stem, cingulate-gyrus, left-amygdala and precentral-gyrus. MDD-individuals at HR showed increased MD in frontal-gyri, cingulate-gyrus, precentral and postcentral-gyrus, and subcallosal-cortex compared to LR group (Fig.1). No difference was found in the exam (1) or (4).
Conclusions: Microstructural abnormalities of WM may underlie the importance of family risk status associated with the development of MDD and thus serve as an endophenotype for the disorder.

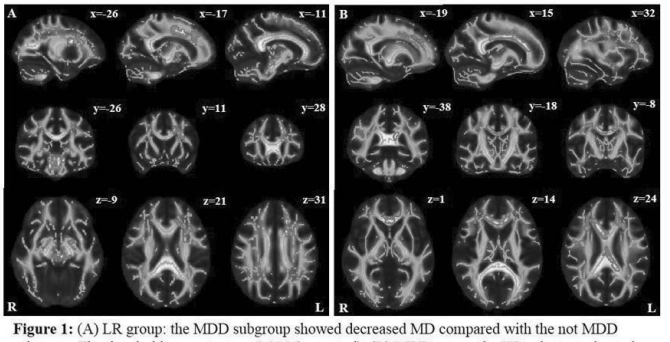

Figure 1: (A) LR group: the MDD subgroup showed decreased MD compared with the not MDD subgroup. The threshold was set at p < 0.035 (corrected). (B) MDD group: the HR subgroup showed increased MD compared with the LR subgroup. The threshold was set at p < 0.04 (corrected). x, y, z denote the coordinates in MNI standard space. L = left, R = right.

Keywords: Tract-Based-Spatial-Statistics (TBSS), familial risk, DTI, developing major depressive disorder
Supported by: 5 R01 MH036197-28; The Sackler Institute at Columbia University; China Scholar Council; China NSF 71471734

289. Ictal EEG Correlates of Neurocognitive Outcome in Electroconvulsive Therapy and Magnetic Seizure Therapy

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Background: There is great interest in identifying biomarkers of neurocognitive effects after electroconvulsive therapy (ECT) and magnetic seizure therapy (MST). Previous research attempts to identify EEG biomarkers of neurocognitive outcome associated with ECT have been inconclusive.
Methods: Patients were participants in a two-center, randomized controlled trial that contrasted the antidepressant efficacy and neurocognitive effects of ultrabrief pulse right unilateral ECT and circular coil MST. Four-channel ictal EEG was recorded during each treatment from 15 ECT and 17 MST patients. EEG electrodes were placed on the Fp1, Fp2, P3, and P4 sites, and were referenced to the ipsilateral mastoids. Discrete wavelet transform was performed using the 4th-order Daubechies wavelet, which decomposed the EEG into delta, theta, alpha, and beta frequency bands. A neurocognitive battery was administered at baseline and post treatment course. We used mixed-effects linear regression models to assess associations between ictal EEG power and neurocognitive outcome.
Results: In ECT, decreased performance on the Mini Mental State Examination (global cognitive function) correlated with increased ictal EEG alpha ($r=-0.18$, $p=0.03$) and theta ($r=-0.23$, $p=0.005$) power. Decreased performance in the Rey Auditory Verbal Learning Test (RAVLT) delayed recall (anterograde memory) correlated with alpha ($r=-0.26$, $p=0.01$) and theta ($r=-0.08$, $p=0.04$) power. In MST, increased RAVLT intrusive recall errors correlated with increased early ictal theta power ($r=0.29$, $p<0.01$).
Conclusions: Increased ictal alpha and theta power correlated with worse cognitive performance following ECT and MST. This is consistent with associations between increased alpha and theta activity, mild cognitive impairment, and Alzheimer's disease. EEG may provide a potential biomarker of neurocognitive effects of seizure therapy.

Keywords: EEG, electroconvulsive therapy, magnetic seizure therapy, neurocognitive outcome, biomarker
Supported by: Stanley Foundation

290. Functional Networks Driven by Transient Activity in Resting-State of Mood Disorders

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Background: Abnormal brain activity during resting state in mood disorder patients is commonly observed and assumed to result from dysfunction in emotion regulation and thought control (rumination). Here, we used a novel data-driven method that identifies spontaneous co-activation patterns reflecting transient changes in brain activity.
Methods: 31 mood disorder patients (9 MDD, 22 BD in various thymic states) and their matched healthy controls underwent resting-state functional MRI resting. Using total activation methodology, we recovered transient brain activation patterns and investigated their duration, occurrence and correlations with clinical parameters in the two groups.
Results: Compared to controls, patients showed decreased spontaneous coactivation patterns of the rostral anterior cingulate areas with amygdala and insula. In terms of dynamics, an increased duration of the anterior components of the default mode network (DMN) was revealed in patients and positively correlated with depression, anxiety, and rumination scores. Controls showed a longer duration of the posterior DMN components, which negatively correlated with the same scales. Finally, patients displayed a positive correlation between DMN duration and level of depression, which was not found in controls.
Conclusions: These findings suggest altered transient_and thus dynamic_brain activity in mood disorder patients at rest. They add argument in favor of less efficient emotional control in patients, and confirm the persistence of DMN activity as a central feature of mood disorders, with dissociation between anterior and posterior midline cortical components directly related to depression, anxiety and rumination symptomatology.

Keywords: resting state, mood disorders, DMN, total activation, fMRI
Supported by: Swiss National Research Foundation

291. Bipolar Disorder and Anxiety Disorders Show Overlapping Functional Neural Signatures

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Background: There is considerable evidence for increased comorbidity between bipolar disorder (BD) and anxiety disorders (AD). Epidemiological studies suggest that up to 45% of patients with BD may meet lifetime criteria for comorbid AD. There is less information about whether this association between BD and AD reflects shared neural underpinnings. The aim of this study was to synthesize evidence from functional magnetic resonance imaging (fMRI) studies in BD and AD to investigate whether there is support for their association at the level of neural circuitry.
Methods: We conducted voxel-based quantitative meta-analysis of the anatomical coordinates of activation from 93 fMRI studies that employed affect processing paradigms and that compared healthy individuals to patients with BD or AD (combining studies of generalized anxiety and panic disorders).
Results: Abnormal hyperactivation in the amygdala/parahippocampal gyrus complex, ventral anterior cingulate, the insula and thalamus was observed both in BD and AD. Additionally, both disorders showed decreased activation in the inferior frontal gyrus and the caudate.
Conclusions: Our findings suggest that during affect processing the most consistent abnormalities in BD and AD implicate the same key nodes of the affect processing circuitry and provide a biological explanation for the observed clinical comorbidity.

Keywords: Neuroimaging, Bipolar, Anxiety, Metaanalysis

292. Functional Connectivity of the Habenula in Relation to Subclinical Depressive Symptoms

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Background: Converging evidence suggests the habenula (Hb) suppresses midbrain monoaminergic reward signaling and may be important in major depression (MDD). The Hb responds strongly to punishment and negative-reward predictors across species, while Hb stimulation in rodents impacts depression-like behaviors. Furthermore, deep brain stimulation of the Hb in two MDD cases was associated with improved symptoms. However, the small size of the human Hb has limited in vivo investigations. Using high-resolution BOLD fMRI data from the Human Connectome Project (HCP), we examined relationships between resting-state functional connectivity of Hb circuitry and subclinical depressive symptoms

Methods: Thirty subjects were chosen from the HCP 500 Subject Release dataset with the 15 highest and 15 lowest NIH Toolbox Sadness ratings. Functional connectivity of the bilateral Hb was assessed via the SPM CONN toolbox at the p<0.005 significance threshold using preprocessed 3T resting-state fMRI data (4x15 minutes concatenated).

Results: We found robust Hb connectivity with the contralateral Hb and bilateral insula. This pattern was stronger in the high-Sadness group, which also demonstrated midbrain Hb connectivity. In contrast, the low-Sadness group exhibited significantly stronger Hb connectivity with posterior cingulate, medial prefrontal cortex, and posterior hippocampus.

Conclusions: High-resolution fMRI revealed expected patterns of Hb connectivity with the contralateral Hb and midbrain. Stronger connectivity within this network in the high-Sadness group supports the model of greater Hb influence in depression. Stronger connectivity between the Hb and default mode network in the low-Sadness group suggests that interactions between Hb circuitry and regions involved in internally-directed cognition may protect against depressed mood.

Keywords: Habenula, fMRI, Depression, Human Connectome Project, Functional Connectivity

Supported by: UL1TR000067; 1U54MH091657; Le Foundation; APIRE/Janssen Foundation; Brain and Behavior Research Foundation

293. Increased Ventricular Lactate in Adolescents with Major Depressive Disorder

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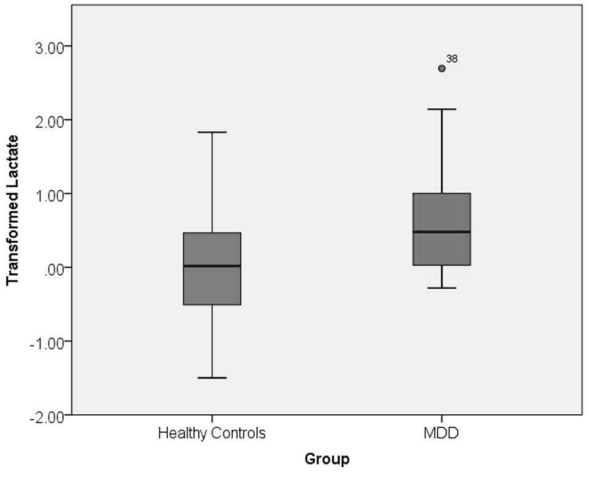
Background: Major depressive disorder (MDD) often starts during the critical developmental period of adolescence. However, limited research has assessed the neurobiological correlates of MDD early in its course prior to the accumulation effects of aging and chronicity. Here, we examined ventricular cerebrospinal fluid lactate, a byproduct of inflammatory neurotoxicity and oxidative stress, in depressed adolescents. We hypothesized that lactate would be increased in depressed adolescents and related to both anhedonia and fatigue.

Methods: Ventricular lactate levels were measured using proton magnetic resonance spectroscopy in nineteen adolescents with MDD (mean age = 17.69, SD = 2.19) and 25 healthy controls (mean age = 15.75, SD = 2.02). Group differences in lactate were assessed using analysis of covariance, controlling for age, while Spearman's correlations assessed the relations between lactate, anhedonia, and fatigue.

Results: The groups did not differ in ventricular volume (U = 231, p = .89), but compared to healthy controls, adolescents with MDD had increased lactate ($F(1,41) = 6.98$, p = .01; Figure 1). Despite these group differences, ventricular lactate was not correlated with anhedonia ($r_s(19)$= .31, p = .19) or fatigue ($r_s(16)$ = .44, p = .086).

Conclusions: These findings may suggest that ventricular lactate, a byproduct of inflammatory neurotoxicity, may be a general biomarker for neuroplasticity impairment, as it appears to be a non-specific correlate of psychiatric illness in adolescents with MDD.

Figure 1



Keywords: Lactate, Major depressive disorder, MRS imaging, Adolescence

Supported by: R01MH095807

294. Predictive Value of Structural MRI in Major Depressive Disorder Outcomes: A 5-year Follow-up

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Background: Major depressive disorder (MDD) is currently thought of as an episodic disorder. Previous studies have reported clinical factors involved in recurrences/relapses. However, only few of them have combined clinical and neuroimaging data to predict long-term outcomes, i.e., remission, relapse or recurrence. Aim: to investigate the usefulness of volumetric brain characteristics to predict the clinical evolution of patients with MDD who were scanned and then followed-up.
Methods: Sixty-six individuals with MDD underwent MRI. Forty-nine were re-evaluated five years later. Patients were categorized as Recovered; Partial-Remitted; Remitted-Recurrent; and Chronic. Voxel-Based Morphometry and FreeSurfer were used to obtain volumetric differences. Polytomous Universal Model -PLUM- regressions were carried out to predict current outcome categories using past demographic/clinical information and gray matter volumes (GMV).
Results: Insula, frontal and cingulate areas showed significant differences in whole-brain VBM analysis and were included as regressors. The regression model with demographic/clinical data explained 32.4% of variance ($\chi2=15.1$; df=3; p=0.002), including HDRS (regression coefficient, cc=0.122; p=0.014), number of MDD-episodes (cc=0.825; p=0.026) and previous illness stage (at scanning moment; cc=1.253; p=0.053). Explained variance was 52% after including brain areas ($\chi2=27.79$, df=6, $p<0.001$). Significant regressors were: duration of illness (cc=0.007; p=0.044), HDRS (cc=0.14; p=0.013), right inferior frontal gyrus (cc=0.002; p=0.042), anterior cingulate (cc=–0.003; p=0.005) and right middle frontal gyrus (cc=–0.001: p=0.066).
Conclusions: the results suggest that structural neuroimaging shows some potential as a prognostic biomarker. Particularly, anterior cingulate, inferior frontal and, to a lesser extent, middle frontal gyri GMV display a predictive capacity together with demographic/clinical information of the long-term MDD outcomes.

Keywords: Major depressive disorder, Structural MRI, Prognosis, Biomarker
Supported by: PI13/01057

295. Pattern Recognition of Brain Activity Related to Clomipramine in Healthy Individuals

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Background: Antidepressants are used to treat anxiety and mood disorders. However a substantial portion of patients do not respond adequately. Many efforts have been directed towards the recognition of biological markers of their effects. Functional magnetic resonance imaging (fMRI) has been used to map antidepressant effects on the brain. Single vector machine (SVM) pattern classification allow unsupervised and exploratory approach tool in this field.
Methods: The present study used fMRI data collected during induction irritability, happiness and neutral states of 10 unresponsive subjects who participated in a four-week not controlled single-blind trial with low doses (30-40mg/day) of clomipramine. Responsiveness was defined as positive changes in at least 3 fields of a schedule: interpersonal, efficiency, mood and self-evaluation. All subjects were scanned at the end of trial and four weeks after. Individual images were used to differentiate patterns between medicated state and washout by VSM method.
Results: Significant accuracy was obtained through the voxel-by-voxel pattern differentiation of clomipramine vs. washout: 0.7 to irritability states and 0.75 to the happy-neutral difference. The occipital, temporo-parietal, dorsomedial and anterior frontal and cingulate gyrus were the main areas to discriminate the medication status.
Conclusions: Distinction patterns resemble our previous findings. The study indicates that SVM method was able to identify with reasonable accuracy functional brain effects of an antidepressant for negative emotional states as well as for positive states when compared to neutral ones. Also, it gives additional basis for the study of biological markers of neural effect of antidepressants even in healthy subjects.

Keywords: fMRI, SVM, antidepressant trial, healthy subjects
Supported by: FAPESP, São Paulo Research Foundation

296. Hippocampal Inflammation and Depressive Symptoms are Associated to the Strength of Hippocampal Functional Connectivity in Multiple Sclerosis: A Study with TSPO-PET and Resting-State fMRI

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Background: Depression is a common co-morbidity of Multiple Sclerosis (MS) and may be a consequence of chronic neuroinflammatory pathology. We have observed that hippocampal neuroinflammation, assessed using PET and the TSPO radioligand 18F-PBR111, is associated with depression in MS patients. Here we explored whether hippocampal inflammation and depressive symptoms severity in MS patients explained variance in the strength of hippocampal functional connectivities to other brain regions.
Methods: Eleven relapsing-remitting MS patients underwent 18F-PBR111 PET and resting-state fMRI. We analysed the correlations of hippocampal functional connectivity to hippocampal 18F-PBR111 Distribution Volume Ratio (DVR) and BDI-II scores. An atlas-defined bilateral hippocampal ROI was used as seed region. The model included hippocampal 18F-PBR111 DVR and BDI-II scores as regressors of interest while controlling for age, disease duration, and neurological disability.
Results: There was high overlap between loci of correlation of hippocampal functional connectivity to hippocampal 18F-PBR111 DVR and those with correlation of hippocampal functional connectivity to BDI scores. Loci with positive correlations were localised in the frontal lobe, including subgenual cingulate and orbital gyrus

cortex, parietal lobe (precuneus, posterior cingulate), and occipital lobe. Loci with negative correlations included insula, other frontal lobe areas, and putamen.
Conclusions: These results, using combined TSPO PET and resting-state fMRI, provide novel insight into the relationship between hippocampal pathology and depressive symptoms in MS and support a pathogenic role for hippocampal microglial activation in the genesis of depression. This paradigm may have broader implications for major depressive disorder in other contexts.

Keywords: Hippocampus, Multiple Sclerosis, TSPO, functional connectivity, depression
Supported by: Wellcome Trust/GSK Training Fellowship

297. Brain Response to Emotion in Adolescents with Non-Suicidal Self-Injury

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Background: Non-suicidal self-injury (NSSI) is a common behavior in adolescents with serious consequences but very limited treatment options. Advancement in treatment development will require an improved understanding of the underlying brain abnormalities. This fMRI study investigated brain activation in response to overt and covert emotion stimuli in adolescents with and without NSSI.
Methods: Adolescents aged 13-21 years with NSSI (n=21) and healthy participants (n=12) completed clinical assessment (including the Toronto Alexithymia Scale [TAS], Symptom Checklist 90 [SCL-90], and Beck Depression Inventory [BDI]) and two MRI scans (both involved happy and fear faces; one with covert stimuli and other with overt stimuli.) Brain imaging analyses (1) identified significantly activated voxels in response to emotional stimuli, (2) compared brain activation to each emotion condition between groups, and (3) examined correlations between activation in significant clusters and clinical variables.
Results: Adolescents with NSSI showed greater brain activation in response to covert happy faces than controls in thalamus, frontal and occipital cortex. There were no group differences for the other emotion conditions. In the NSSI group, thalamus activation correlated positively with TAS score and negatively with SCL-90 anxiety and positive symptom distress index scores, and BDI subscores for self-dislike and self-criticalness. Frontal activation correlated negatively with SCL-90 depression, anxiety, global severity index and PSDI scores.
Conclusions: Abnormal automatic detection of positive emotion in the NSSI group may underlie these adolescents' difficulty identifying and describing emotions, and could represent a future treatment target.

Keywords: adolescent, non-suicidal self-injury, self-harm, fmri
Supported by: UL1TR000114;1P60MD003433;R21MH094558

298. Subgenual Anterior Cingulate Cortex Volume in Depressed Youth: The Role of Comorbidity and Age

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Background: Major depressive disorder (MDD) onset often occurs during adolescence. However, there is a paucity of data describing how MDD and commonly associated comorbid disorders alter neurodevelopmental trajectories. We examined subgenual anterior cingulate (sgACC) morphometry in youth with MDD. The sgACC is important in aspects of emotional and reward processing, and tends to be structurally altered in depressed adults. We assessed whether sgACC volume is affected by comorbidity and whether age influences volume through adolescence.
Methods: Structural magnetic resonance imaging (MRI) scans (1.5 & 3T) and clinical assessments (Hamilton Rating Scale for Depression [HAMD17]) were obtained from a total of 68 participants with MDD and 64 controls (11-25 years) at two sites. Of those with MDD, 32 had a comorbid anxiety disorder. Investigators blind to diagnoses manually traced the sgACC to obtain volume measures (mm3).
Results: No group differences were apparent in sgACC volume but MDD participants with (vs. without) comorbidity had smaller volumes, even after controlling for HAMD17 scores. Overall, a positive correlation existed between sgACC volume and age while an inverse correlation existed between volume and HAMD17 scores. When split by group, these correlations were only evident in the MDD cohort.
Conclusions: Psychiatric comorbidity in depressed youth was associated with decreased sgACC volumes suggesting delayed or altered neural development in a key emotion regulation region. Participants with the most severe depression symptoms also had small sgACC volumes compared to those with less severe symptoms, suggesting a link between structure and clinical features.

Keywords: depression, adolescence, sgACC, comorbidity, age

299. Reductions in Superior Temporal Gray Matter Volume in High-Risk Bipolar Offspring

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Background: Bipolar disorder (BD) has been associated with gray matter volume (GMV) abnormalities in a number of brain regions including prefrontal, temporal and cingulate cortices. Few studies have investigated GMVs in at-risk bipolar offspring, of these, no studies have investigated GMVs in a symptomatic population of bipolar offspring.
Methods: We recruited children with one parent diagnosed with BD (I or II) , between 8-16 years of age, and could be asymptomatic or symptomatic (presenting with symptoms of depression, anxiety and/or ADHD, but not BD). All children underwent a di-

agnostic interview (KSADS-PL) and a T1 weighted MRI scan (GE 3T). Freesurfer software was used to generate gray matter and white matter boundaries and GMVs were calculated for 14 a priori defined regions.
Results: Thirty high-risk offspring (13 asymptomatic, 17 symptomatic, 13.8±2.8y, 43%F) and 20 age-, sex- and IQ-matched healthy controls (13.3±2.5y, 45%F) have completed the study. Of these, a subset of 32 subjects (18 high-risk, 14 healthy controls) were analyzed to date. Compared to healthy controls, high-risk offspring showed decreased volume in the right superior temporal gyrus (pcorr < 0.05).
Conclusions: Preliminary analyses have identified GMV differences in the superior temporal gyrus, a region that has been previously implicated as functionally significant in children and adolescents diagnosed with BD.

Keywords: Gray Matter Volumes, Neuroimaging, Bipolar Offspring, Bipolar Disorder
Supported by: NARSAD

300. The BDNF Val66Met Polymorphism, Resting-state Hippocampal Functional Connectivity and Cognitive Deficits in Acute Late-onset Depression

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Background: To investigate the regulating effect of the BDNF gene to the cognition-related hippocampal functional connectivity (HFC) in late-onset depression (LOD).
Methods: 26 LOD patients and 33 normal controls (NCs) completed clinical assessments, neuropsychological testing, provided blood samples for genotyping, and underwent resting-state functional MRI scans. Seed-based correlation analyses and two-way analysis of covariance were performed to explore the main effects and interactive effects of LOD and BDNF Val66Met polymorphism on the HFC. Spearman correlation was applied to examine the cognitive and emotional significance of these altered HFC networks.
Results: Compared with NCs, bilateral positive HFC with the right insula, left positive HFC with bilateral orbit-frontal cortex (OFC) and left precuneus, right positive HFC with right dorsolateral prefrontal cortex were disrupted, and bilateral negative HFC with right postcentral gyrus were reversed in LOD patients. On the other hand, BDNF Met allele mainly damaged bilateral positive HFC with the cerebellum. Besides, the changed HFC with the OFC, postcentral gyrus and cerebellum significantly correlated to the cognitive deterioration. However, the interactive effects of LOD and BDNF Met allele primarily influenced the bilateral HFC with the temporal cortex and dorsal nexus. These interactive effects indicated an antagonistic action between the BDNF Met allele and LOD. Unfortunately, there was no significant association between the depressive severity and any altered HFC networks.
Conclusions: The changed HFC with the OFC, postcentral gyrus and cerebellum may contribute to cognitive deterioration. The BDNF Met allele may play a protective role in the HFC network with the temporal cortex and the dorsal nexus in LOD patients.

Keywords: Late-onset depression, BDNF Val66Met, resting state fMRI, hippocampi, cognition
Supported by: National Natural Science Foundation of China (81371488, Yonggui Yuan)

301. Seasonal Variation in Serotonin Transporter Binding in Seasonal Affective Disorder and Health: A [^{11}C]DASB Positron Emission Tomography Study

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Background: Seasonal Affective Disorder (SAD) affects 1-6% of people in regions of more Northern or Southern latitude. 5-HTT BP_{ND}, an index of 5-HTT levels measured with [^{11}C]DASB positron emission tomography (PET), is higher throughout the brain in winter relative to summer in health and this is a well replicated finding. It was hypothesized that seasonal change in 5-HTT BP_{ND} would be greater in individuals with SAD relative to healthy volunteers.
Methods: 12 SAD (μ: 32.4yrs) and healthy participants (μ: 29.0yrs) underwent [^{11}C]DASB PET scans in both summer and winter, in randomized order, to measure seasonal change in 5-HTT BP_{ND}. Regions assayed included the prefrontal cortex, anterior cingulate cortex, thalamus, putamen, temporal cortex, midbrain and striatum.
Results: A global elevation in 5-HTT BP_{ND} was observed in winter relative to summer in SAD as compared to health (magnitude 17% vs. -0.3%, univariate ANOVA, $F_{1,22}$=4.83, p=0.039). A similar trend was also detected in individual brain regions assayed ($F_{1,22}$=2.07-4.26, p=0.05-0.16). In the prefrontal cortex, a positive correlation was observed between severity of SAD (measured with the Seasonal Pattern Assessment Questionnaire) and seasonal change in 5-HTT BP_{ND} (r=0.576, p=0.05).
Conclusions: Overexpression of the 5-HTT is associated with reduced extracellular serotonin and [^{11}C]DASB has strong preferential binding for the 5-HTT on outer cell membranes. Since greater seasonal fluctuation in 5-HTT BP_{ND} is associated with SAD, and the severity of SAD, this suggests that fluctuation in levels of 5-HTT, most likely in the prefrontal cortex, represents a component of the phenotype of SAD.

Keywords: seasonal affective disorder, serotonin transporter, positron emission tomography, prefrontal cortex
Supported by: Canadian Institutes of Health Research (CIHR); Brain Canada (studentship)

302. Neuroinflammation and Glutamate/Glutamine: Preliminary [18F]-FEPPA PET and 1H-MRS Study in First Episode Unmedicated Patients With Schizophrenia

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Background: Both glutamatergic dysfunction and neuroinflammation have been hypothesized to be involved in schizophrenia pathophysiology. Furthermore, glutamatergic dysfunction may contribute to the neuroinflammatory process, providing a potential link between these two systems. In the present study, we examined the association between the level of neuroinflammation and the level of glutamate and glutamine (Glu+Gln) in the prefrontal area in first episode psychosis (FEP).
Methods: 5 FEP were scanned with HRRT PET to examine the total volume of distribution (VT) of second generation TSPO PET radioligand [18F]-FEPPA, and subsequently obtained the Glu+Gln metabolite levels using magnetic resonance spectroscopy (MRS) with 3T MRI in the pregenual anterior cingulate cortex (pgACC). The PET data was analyzed using a 2-tissue compartment model and the MRS data was analyzed with LCmodel.
Results: In the pgACC, a non-significant trend of higher Glu+Gln levels was found in participants with higher neuroinflamamtion (VT) (Spearman's rho=0.70, p=0.19). Implications of these preliminary findings for symptoms and neuropsychological deficits will be explored.
Conclusions: Preliminary results suggest that a positively correlating trend may exist between neuroinflammation and the level of glutamatergic dysfunction in the prefrontal area in early stage of psychosis.

Keywords: Neuroinflammation, Glutamate, PET, MRS, Schizophrenia
Supported by: 1R01MH100043-01A1

303. Dopamine D2 and D3 Receptor Availability in Antipsychotic-free patients with Schizophrenia in Later Life: A Cross-sectional [11C]-(+)-PHNO and [11C]-raclopride PET Study

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Background: Schizophrenia is a life-long illness requiring maintenance antipsychotic treatment across the life span. Age-related changes in dopamine D2/3 receptor (D2/3R) are expected to result in enhanced antipsychotic sensitivity as patients grow older. However, no study has examined D2R and D3R availability in antipsychotic-free patients with schizophrenia in later life.
Methods: Our study included patients with schizophrenia, ≧50 years, and having been antipsychotic-free for at least 2 weeks. We compared the non-displaceable binding potential (BPND) of [11C]-raclopride and [11C]-(+)-PHNO between patients and sex- and age-matched controls (n=11). ROIs included caudate, putamen, and ventral striatum for [11C]-raclopride and [11C]-(+)-PHNO, and globus pallidus, substantia nigra, hypothalamus, and ventral pallidum for [11C]-(+)-PHNO.
Results: In total, 11 patients participated: 5 females, 4 antipsychotic-naïve and 7 antipsychotic-free, age=66.0±11.0 years, duration of illness=37.0±20.0 years, duration of untreated illness=2.2±4.0 years, PANSS score=82.6±27.5. 10 participants were scanned with [11C]-raclopride, and 7 with [11C]-(+)-PHNO [6 with both radiotracers]). No differences were found between antipsychotic-free patients and healthy controls in the BPND in any of the ROIs (F(1,72)=.00, p=.96 for [11C]-raclopride; F(1,80)=.79, p=.38 for [11C]-(+)-PHNO, respectively). The [11C]-raclopride BPND in ventral striatum inversely correlated with PANSS positive and negative subscale scores (r=-.66, p=.04; r=-.68, p=.03, respectively).
Conclusions: Our study is the first to explore D2R availability using antagonist ([11C]-raclopride) and agonist ([11C]-(+)-PHNO) PET radiotracers, and D3R availability using [11C]-(+)-PHNO in patients with schizophrenia in later life. The preliminary results suggest no differences in D2R and D3R availability in patients with schizophrenia in later life in comparison with healthy controls.

Keywords: schizophrenia, PET, dopamine, geriatric, D3
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304. Stress-induced Prefrontal Dopamine Release in the Early Stage of Psychosis: A Preliminary Report

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Background: The underlying neurobiological alteration that leads to increased vulnerability of developing psychosis remains unclear. Stress plays a key modulatory role in dopaminergic system which is critical to the pathogenesis of psychosis, yet stress-induced dopamine release in prefrontal cortex (PFC) in psychosis remains unexplored. The current study aims to examine the effects of stress PFC dopamine release in drug-naïve schizophrenia (SCZ) and clinical high risk for psychosis (CHR) as compared to matched healthy volunteers (HV).
Methods: To examine stress-induced dopamine release outside the striatal regions, we used a very high-affinity dopamine D2/3 PET radiotracer: [11C]-FLB 457. Stress-induced DA release under a validated psychosocial stress task was estimated as the percent change in binding potential between conditions (stress and control scan) in the PFC areas.
Results: 10 HV, 8 CHR and 8 SCZ subjects, with clear urine drug screens, were included so far. We found a preliminary significantly higher displacement of [11C]-FLB457 in SCZ patients in the anterior cingulate after controlling the binding potential in the control scan (F=3.60, df=2,22, p=0.04), while the difference

between CHR subjects and HVs was non-significant. A non-significant trend of positive association was observed between the level of displacement and severity of positive psychotic symptoms (r=.67) in SCZ patients.
Conclusions: A higher dopamine release under social stress was found in anterior cingulate in drug-naïve SCZ. While the data is still preliminary, the finding purposes that in the early stage of psychosis, a sensitized prefrontal DA response to social stress may exist. Larger sample sizes are warranted.

Keywords: Psychosis, Stress, Clinical high risk, Dopamine, Positron Emission Tomography
Supported by: CIHR Operating Grant 2013 for Dr Romina Mizrahi

305. Cannabis Use in Schizophrenia: Investigating Circuit Level Functional Connectivity

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Background: Cannabis use disorder (CUD) is common in schizophrenia (SCZ) and significantly worsens patient outcomes. Nonetheless, cannabis use in SCZ has been associated with improved cognition. Development of therapeutics will be facilitated by elucidation of the effects of cannabis use on brain circuitry. We investigated resting state functional connectivity (rsfc) of the brain reward circuit (BRC), default mode network (DMN) and task positive network (TPN) in patients with SCZ/CUD, and assessed the effects of smoked cannabis and oral tetrahydrocannabinol (THC) on these networks. We also evaluated the association between connectivity and working memory.
Methods: 12 patients with SCZ/CUD (abstinent > 7 days) and 12 controls completed fMRI resting scans before and after smoking a 3.6% THC cannabis cigarette or ingesting 15 mg oral THC. Correlations within the BRC, DMN, and TPN were assessed using seed-to-voxel rsfc.
Results: Decreased connectivity in the BRC, DMN hyperconnectivity, and reduced DMN-to-TPN anti-correlation were seen in patients vs. controls. Cannabinoid agonists increased connectivity within BRC and the DMN-to-TPN anticorrelation. The degree of anticorrelation was associated with working memory performance. Cannabis lowered and THC increased DMN hyperconnectivity.
Conclusions: These data suggest reward dysfunction may contribute to cannabis use in SCZ, and that cannabis (or THC) use may improve such dysfunction. Cannabinoid induced enhancement of DMN-to-TPN anticorrelation, and its association with working memory performance may explain why cannabis-using patients with SCZ have improved cognition. These findings suggest that, although cannabis use worsens SCZ outcomes, low dose cannabis may improve BRC connectivity, DMN-TPN anticorrelation, and working memory. Further studies are needed to confirm these preliminary findings.

Keywords: Schizoprenia, Cannabis use disorder, Default mode network, functional connectivity, brain reward circuit
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306. Neural and Affective Reactivity to Positive Stimuli Following D-Amphetamine Differ by *COMT* Val[158]Met Genotype

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Background: There are individual differences in the neural, cognitive, and affective effects of d-amphetamine. Genotype of the *COMT* Val[158]Met polymorphism is associated with variability in dopaminergic tone and is relevant to between-person variation in the drug effect. We examined the association between *COMT* genotype and affective and fMRI BOLD responses to emotional stimuli after administration of d-amphetamine, using a placebo controlled, double-blind, within-subjects cross-over design.
Methods: Thirty-one (*N*=31) healthy young adults were administered placebo and d-amphetamine (20 mg) on two separate study days. Participants viewed positive, negative, and neutral IAPS images in a blocked fMRI design on each day, and *COMT* Val[158]Met (rs4680) genotype associations were assessed in a region-of-interest analysis.
Results: A significant three-way interaction between drug condition, IAPS image valence, and *COMT* genotype was identified in right parahippocampal gyrus (ANOVA $F(4,56)=2.73$, $p<0.05$). Met/Met individuals exhibited a significant decrease in reactivity to positively valenced stimuli after amphetamine ($p=0.01$) and, post-drug administration, had the lowest response among the genotype groups (p's<0.02). Val-allele carriers did not show altered responsiveness following the drug ($p>0.2$). However, self-reported affect did not follow the same pattern: in fact, Met homozygotes reported the highest positive affect ratings across groups and exhibited a marginal drug-related increase ($p=0.07$).
Conclusions: Healthy adults who are Met/Met homozygotes showed amphetamine-induced reductions in fMRI BOLD response in a specific brain region – the right parahippocampal gyrus – that is involved in emotional memory encoding and retrieval, relative to Val-carriers. This could reflect neural efficiency or possibly a drug-related blunting of reactivity in this group.

Keywords: Imaging genetics, Amphetamine challenge, COMT Val/Met, Individual differences
Supported by: R01DA020725

307. Spectroscopy Differences Between at Risk Populations for Psychosis: A 22q11DS Versus UHR Patients Comparison

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Background: 22q11 deletion syndrome (22q11DS) and Ultra High Risk patients both have approximately 30% risk to develop psychosis. Proton magnetic resonance spectroscopy (1H-MRS) studies have shown abnormalities in brain metabolites in dorsolateral prefrontal cortex (DLPFC) and hippocampus in both 22q11DS and UHR patients. We hypothesized that their different risk profiles are associated with specific differences in brain metabolites between these groups.
Methods: We recruited 13 non-psychotic 22q11DS patients, 16 UHR patients and 16 controls. UHR patients were younger than 22q11DS but matched to controls. No participants used antipsychotics. Brain metabolites were measured with 1H-MRS in the DLPFC and hippocampus and compared with t-tests.
Results: DLPFC glutamine was higher in UHR compared to 22q11DS (p=0.036), but non-significant after co-varying for age and gender. Other brain metabolites did not differ significantly between the 22q11DS and UHR groups.
UHR patients compared to controls had lower glutamine+glutamate (GLX) in the HIP (p=0.50).
Conclusions: UHR and 22q11DS patients did not show robust differences in brain metabolites. This may be due to limited power or may reflect that brain metabolites are comparable between the risk profiles. Lower hippocampal glutamine+glutamate in the HIP of UHR patients is an interesting novel finding, in light of evidence of higher hippocampal glutamine+glutamate in schizophrenia patients.

Keywords: UHR, 22q11ds, spectroscopy
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308. Abnormalities in Corpus Callosum in Subjects with 22q11 Deletion Syndrome and with Positive Psychotic Symptoms

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Background: Individuals with 22q11Deletion Syndrome (22q11DS) have a 40% incidence of psychosis and represent a population at high-risk to develop schizophrenia. The corpus callosum (CC) is a major interhemispheric fiber. Abnormalities in CC were reported in subjects with 22q11DS and in schizophrenia patients, however it is not known how early these changes occur.
Methods: Diffusion Magnetic Resonance Images (dMRI) of the brain white matter were acquired from 39 subjects with 22q11DS (including 8 subjects with positive psychotic symptoms), and 22 matched controls, age 20.5 +/-1.8 years. Psychotic symptoms were assessed by Brief Psychiatric Rating Scale (BPRS). The whole CC and the posterior subdivision of the CC, namely the fibers connecting the parietal-temporal-occipital regions, were reconstructed using tractography. DMRI measures, fractional anisotropy (FA) and mean diffusivity (MD), were compared between the participant groups. A neuropsychological battery was administered.
Results: Subjects with 22q11DS, when compared to controls, had reduced MD in the whole CC (p=0.001), but not in the most posterior subdivision of the CC. On the contrary, the 22q11DS subgroup with psychotic symptoms had reduced MD in the whole CC (p=0.030), as well as in the posterior part of the CC (p=0.019). In the 22q11DS group with positive symptoms of psychosis, MD measures extracted from the posterior part of the CC correlated with scores on visual memory, measured in part by Visual Span Forward (r=0.820, n=7, p=0.020).
Conclusions: Abnormalities in posterior part of the CC were observed in young adults with 22q11DS prior to schizophrenia onset. The abnormalities correlated with poorer performance on visual memory

Keywords: 22q11deletion syndrome, psychosis, visual memory, diffusion Magnetic Resonance Imaging (dMRI), corpus callosum
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309. Neural Correlates of a Five-factor Model of Psychosis

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Background: While heterogeneity among psychosis presentations is widely appreciated, the associated variance in neural circuits underlying symptom heterogeneity remains unknown. Knowledge of symptom-circuit relationships could help reveal disease mechanisms, disorder subtypes, and new treatment targets.
Methods: We derived symptom dimensions using confirmatory factor analysis of clinical symptom scales in a large sample of patients with a psychotic disorder (n=1137) and then, in a subset of those patients scanned with resting-state fMRI (n=147), regressed individual subject factor loadings against functional connectivity derived using a connectomic approach (7 large-scale cortical networks composed of 122 brain regions).
Results: Five symptom dimensions, consistent with prior reports, included mania, depression, negative symptoms, positive symptoms, and substance abuse. Mania scores were associated with tighter correlation between nodes of the dorsal attention network (DAN) and the default network and frontoparietal control network (FCN), which both typically anticorrelate with DAN. Negative symptoms were associated with tighter correlations in the Ventral Attention Network and Salience Network. Positive symptoms were associated with FCN changes.
Conclusions: Several previously unknown symptom-circuit relationships were revealed by our analysis. For instance, reduced anti-correlation between attentional and association systems occurred in individuals with acute mania and also to a lesser degree in non-manic patients with history of mania. Reduced

anti-correlations may be biological determinants of the mood and cognitive dysregulations of bipolar disorder and may inform illness definition, exploration of underlying mechanisms, and treatment testing and design. Thus, large-scale imaging studies coupled with careful clinical phenotyping can yield useful symptom-circuit relationships that may help understand the biological determinants of clinical heterogeneity in psychosis.

Keywords: psychosis, mania, functional connectivity, factor analysis
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310. Cortical Dopaminergic Deficiency in Schizophrenia While Performing a Cognitive Task

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Background: Despite considerable pharmacological advances in the treatment of positive symptoms of schizophrenia (SCZ), significant lacunae remain in the treatment of cognitive deficits. Although several lines of evidence point towards deficient cortical function in SCZ, no study has directly tested dopamine (DA) deficiency in SCZ. Hence, we examined the neurochemical basis of cognitive symptoms of SCZ using PET in antipsychotic free patients with SCZ.
Methods: Antipsychotic-free SCZ (n=8;6 males) and age, sex matched healthy volunteers (HV) (n=8;5 males) underwent 2 PET scans using [11C]FLB-457, D2/3 receptor ligand while doing the Wisconsin Card Sorting Test (WCST) and a sensorimotor control task (SMCT). Individual MRIs were obtained for image co-registration and Region of interest delineation. Time activity curves were obtained to obtain binding potential non-displaceable (BPND) using the simplified reference tissue model. Percentage change in FLB-457 BPND between conditions, an index of cortical dopaminergic deficiency, was calculated using the formula [(BPNDSMCT-BPNDWCST)/BPNDSMCTX100].
Results: All patients were antipsychotic free for at least 3 months and did not have comorbid psychiatric or substance use disorders. All participants had clean urine drug screens. We found a significant difference between patients and controls in [11C]FLB-457 percent change in the Anterior Cingulate cortex (ACC) (t=2.45; p=0.02), with a trend in dorsolateral prefrontal cortex (DLPFC, (t=1.89;p=0.07). In response to cognitive task SCZ patients (-9.07±14.84) had lesser [11C]FLB-457 percent change than HV (6.77±7.89) in ACC.
Conclusions: This pilot data, if confirmed in a larger study, represent the first in-vivo PET imaging demonstration of cortical dopaminergic deficiency in response to a cognitive task in SCZ.

Keywords: Schizophrenia, Cognition, Positron emission tomography, Dopamine
Supported by: CIHR Canada-Hope scholarship

311. Genetic Variation in Rasd2 Modulates Psychotomimetic Drug Effects in Mice and Schizophrenia-related Phenotypes in Humans

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Background: Rasd2 is a striatal GTP-binding protein which modulates different key neurodevelopmental pathways, including Akt and mTOR. Here, we investigated how Rasd2 and its genetic variation are associated with a series of prefronto-striatal phenotypes related to schizophrenia in rodents and humans.
Methods: We employed 12- week- old Rasd2 knockout mice (Rasd2-/-) and age-matched wild type littermates (Rasd2+/+) to evaluate the involvement of this gene in modulating vulnerability to schizophrenia-like behaviors induced by amphetamine (Amph) and phencyclidine (PCP), such as motor hyperactivity and disruption of prepulse inhibition (PPI) on the startle reflex. Furthermore, we investigated if RASD2 (22q12.3) genetic variation in healthy humans is associated with molecular-to-systems level phenotypes implicated in schizophrenia, including prefrontal and striatal grey matter volume and physiology during working memory (WM), as measured with 3-Tesla magnetic resonance imaging.
Results: Both Amph and PCP triggered in Rasd2-/-mice greater PPI disruption and psychomotor stimulation effects than in wild type animals. Of note, pre-treatment with Haloperidol or Clozapine completely prevented psychotomimetic-induced PPI deficits in both genotype groups. Furthermore, we found that the G allele of a SNP in RASD2 (rs6518956), which was associated with greater RASD2 mRNA expression in human post-mortem prefrontal cortex (N=216), also predicted greater prefrontal grey matter volume (N=150) and prefronto-striatal activity during WM (N=160) in healthy individuals.
Conclusions: Our results suggest that Rasd2 represents a gene of potential interest in psychiatric disorders for its ability to modulate prefronto-striatal phenotypes related to schizophrenia in rodents and humans.

Keywords: rasd2, animal model, psychotomimetics, humans, imaging

312. Genetic Risk for Schizophrenia During Working Memory Computation

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Background: Unaffected siblings of schizophrenia patients may be without confounders of medication and lifestyle differences despite carrying some of the risk-associated genetic variation implicated in cognition and brain function, particularly working memory (WM). Computational aspects of WM, engaging dorsolateral prefrontal (DLPFC) and striatal dopaminergic D2 signaling, may be more affected by disease than information maintenance, and may also be under disease-related genetic influence. We examined correlates of neural signaling in an event-related WM task designed to dissociate computation and maintenance. We studied subjects across genetic risk for schizophrenia, and in relation to correlated neural activity in healthy monozygotic twins.

Methods: 45 healthy controls (HC), 47 schizophrenia patients (SZ), and 40 unaffected siblings (SIB) from the CBDB/NIMH Sibling Study, and 20 healthy monozygotic twins from the Peking University-Lieber Institute Translational Neuropsychiatry Program performed an event-related numerical WM task in 3T MRI scanners. All groups were matched for task performance.

Results: Two-group analyses revealed that HC had increased neural correlates of activity relative to SZ and SIB ($p<0.001$ uncorrected), specifically in events engaging WM computation rather than maintenance. These differences were in DLPFC between HC and SIB, and in DLPFC and striatum between HC and SZ. The DLFPC region overlapped with areas of high intra-class correlation ($r>0.6$) across the monozygotic twin-pairs engaging WM computation.

Conclusions: While WM related brain function during information maintenance and computation is under genetic (and environmental) influence, genetic risk for schizophrenia may be specifically associated with DLPFC signaling deficits during computational rather than maintenance aspects of WM.

Keywords: schizophrenia, computational working memory, siblings, dlpfc

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313. The Details of Structural Dysconnectivity in Psychotic Disorder: A Study of Diffusion Weighted Imaging Measures

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Background: Diffusion Tensor Imaging (DTI) studies in psychotic disorder have shown reduced FA, often interpreted as disturbed white matter integrity. This observed 'dysintegrity' may have different origins, as FA is thought to reflect a combination of myelination, fiber density and number of axons. Disentangling the structural substrate of the diffusion tensor in individuals with (risk for) psychotic disorder can provide details on the underlying microstructural changes, which was the aim of this study.

Methods: From 85 patients with psychotic disorder, 93 siblings of patients and 80 healthy controls, DTI scans were acquired. Group comparisons were performed using Tract Based Spatial Statistics (TBSS) on several DTI measures: axial diffusivity (AXD), radial diffusivity (RD), mean diffusivity (MD), and the case linear (CL), case planar (CP) and case spherical (CS) parameters.

Results: AXD did not differ between the groups. RD and CS values showed significant increases in patients compared to controls and siblings, with no significant differences between the latter. For CL, the opposite was true (smaller in patients than in siblings and controls). MD was increased in patients compared to controls, but not compared to siblings and no difference between siblings and controls. CP was decreased in both patients and siblings compared to controls.

Conclusions: The findings indicate that structural dysconnectivity associated with psychotic disorder is not driven by the number of axons, but rather by myelin alterations, which may be related to increased free water movement. In contrast, decreased fiber orientation and organization may be shared between patients and siblings.

Keywords: Psychotic Disorder, White Matter, Myelin, Dysconnectivity, Diffusivity

314. Magnetic Resonance Imaging of the Fusiform Gyrus in Patients with Childhood-Onset Schizophrenia

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Background: The fusiform gyrus has been strongly implicated in the regulation of facial perception, an essential aspect of social interaction. Abnormalities in the fusiform gyrus have been reported in patients with both autism spectrum disorders (ASD) and schizophrenia, both of which are characterized by compromised ability to form relationships.

Methods: In order to probe the physical basis of these deficits and determine their status as state or trait markers, patients with Childhood-Onset Schizophrenia (COS) (n = 101, 264 scans), a rare and severe form of schizophrenia, their healthy siblings (n = 79, 176 scans), and unrelated healthy volunteers (n = 101, 258 scans) were followed longitudinally with structural MRI scans at two-year intervals. Automated brain imaging software segmented the fusiform gyrus of each individual with resultant gray matter volume (GMV) measurements.
Results: Patients with COS had significantly reduced left, right, and total fusiform gyrus GMV ($p > 0.01$). Healthy siblings of patients with COS did not differ significantly from controls in total fusiform GMV. Lastly, patients with COS/ASD comorbidity (20%) had significantly increased left fusiform gyrus GMV ($p = 0.011$), rate of fusiform gyrus growth ($p = 0.021$) and increased total slope ($p = 0.036$).
Conclusions: These findings highlight the role of fusiform gyrus development in the schizophrenia pathophysiology and suggest that this deficit is more likely to be illness related and unlikely to be a trait marker.

Keywords: COS, Schizophrenia, Fusiform, MRI, Neuroimaging

315. Lack of Default-Mode Network Deactivation in Schizophrenia in Response to Neutral Stimuli: An fMRI Study

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Background: Preliminary functional imaging studies on have intriguingly revealed that hyper-activations of sub-cortical structures (e.g. amygdala, hippocampus & putamen) are observed in schizophrenia patients in response to emotionally neutral stimuli. These results have been interpreted in light of the influential aberrant salience hypothesis of psychosis. Here, we performed a functional imaging study to further our understanding of schizophrenia patients' tendency to assign emotional significance to neutral stimuli.
Methods: Thirty-nine schizophrenia patients (DSM-IV criteria) and 41 healthy controls were scanned using functional magnetic resonance imaging while viewing blocks of emotional (positive and negative) and neutral images, interleaved with rest periods. fMRI data was analyzed with Brain Voyager, 2.0.
Results: For the Neutral minus Rest contrast, both controls and schizophrenia patients activated frontal, parietal, temporal, occipital, sub-cortical and cerebellar regions. However, controls de-activated the default-mode network [ventro-medial prefrontal cortex (vmPFC), anterior and posterior cingulate gyri], whereas schizophrenia patients did not. The schizophrenia-control comparison revealed decreased activations of the ventro-medial prefrontal cortex in controls, relative to patients. Behaviorally, schizophrenia patients assigned more emotional significance to neutral stimuli than controls.
Conclusions: The results of the current functional imaging study show that schizophrenia is associated with a failure to deactivate the ventro-medial prefrontal cortex while viewing neutral material. This result is consistent with the findings from the resting-state literature showing that the default-mode network is impaired in schizophrenia. In theory, a failure to deactivate self-relevancy processes could explain why schizophrenia patients over-estimate the salience of external stimuli lacking biological significance.

Keywords: Schizophrenia, Salience, Default-mode network, fMRI
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316. Thalamo-Striatal Dysfunction May Underlie Co-morbidity Between OCD and Schizophrenia

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Background: Several lines of evidence suggest that obsessive compulsive disorder (OCD) and schizophrenia (SZ) may be related. Patients with SZ have a lifetime risk of 12% for OCD while patients with OCD carry a 6-fold increased risk for developing SZ. Magnetic resonance imaging (MRI) studies suggest that dysfunction within distributed neural networks is central to the pathophysiology of both disorders. In this study we focused specifically on affect processing and tested the hypotheses that OCD and SZ may present with overlapping pathology within the corresponding neural network.
Methods: We conducted voxel-based quantitative meta-analysis of the anatomical coordinates of activation from 299 functional MRI studies comparing healthy individuals to patients with SZ or OCD.
Results: Within the core affect processing network involving the medial prefrontal cortex (PFC) and limbic and paralimbic regions (anterior cingulate, insula, amygdala complex), patients with SZ and OCD showed similar topographic distribution of abnormalities but in the opposite direction. SZ was associated with widespread under- engagement and OCD was associated with overactivation. Additional activation in OCD was also present in the precentral cortex. Both disorders showed hypoactivation in the caudate nucleus and the thalamus.
Conclusions: Our findings highlight dysfunction within the thalamo-striatal system as a possible shared feature between SZ and OCD. This finding is consistent with the role of this system in generating, maintaining and switching between motor and non-motor mental functions.

Keywords: Metaanalysis, OCD, Schizophrenia, Neuroimaging

317. Reward Value of Social Relationships Is Negatively Correlated with Dopamine D2/3 Receptor Availability in the Ventral Striatum of Healthy Humans

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Background: As a social species, engaging in social relationships is fundamental to human well-being. Differences in striatal dopamine (DA) function may be related to both the rewarding value of relationships and drugs of abuse. As measured with positron emission tomography (PET) both socially detached persons and persons with substance use disorders demonstrate reduced DA

D2/3 receptor (D2/3R) availability in the striatum. However, previous PET studies have not examined the relationship between social attachment and D2/3R availability in the ventral striatum (VS). This is pertinent given the integral role of the VS in the formation of social bonds and drug addiction.
Methods: Using the agonist radiotracer [11C]-(+)-PHNO we investigated the relationship between self-reported attachment in thirty-two healthy persons and DA D2/3R availability in the VS.
Results: Surprisingly, more social attachment was related to less [11C]-(+)-PHNO binding in the VS, as measured with the attachment subscale of the temperament and character inventory (r(30)=-.43, p=.01). This relationship held in a subsample who also completed the detachment subscale of the karolinska scales of personality (r(10)=.62, p=.03).
Conclusions: Our findings suggest that persons who are more socially detached have less endogenous DA occupying D2/3R in the VS. These findings have important implications for better understanding the neurochemical systems involved in attachment, and how these systems may be overridden by drugs of abuse.

Keywords: dopamine, PET, attachment, addiction, social
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318. Dopamine Response to Challenge with Corticotropin-Releasing Factor: A PET Imaging Study with Implications for Addictions

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Background: The hormone corticotropin-releasing factor (CRF) is a key component of the neuro-endocrine stress response, and has been implicated in addiction, as it modulates dopamine release in animal models. Here we investigated for the first time whether CRF administration increases dopamine release in humans.
Methods: Six healthy subjects (3M/3F, 32.3 ±8.8 years old) completed two positron emission tomography scans with the displaceable dopamine $D_{2/3}$ receptor radioligand [^{11}C]-(+)-PHNO: Once after saline and once after CRF injection. [^{11}C]-(+)-PHNO binding (BP_{ND}) was estimated in regions of interest: ventral stiatum (VS), dorsal striatum (DS; consisting of anterior and posterior dorsal caudate and putamen), globus pallidus (GP), and substantia nigra (SN). Subjective report and blood samples for the endocrine stress markers ACTH and cortisol were collected in n=5 subjects.
Results: One-tailed paired-samples t-tests revealed that CRF injection decreased BP_{ND} (relative to saline), suggesting CRF-induced dopamine release, in SN (-16%, p=.037) and DS (-11%, p=.035), particularly anterior sectors (putamen -12%, p=.017; caudate -13%, p=.048), but not VS or GP (both -3%, p>.23). Reduced SN BP_{ND} correlated with self-reported stress (p=.01) and decreased appetite (p=.02). Plasma ACTH and cortisol were elevated in the CRF condition (p<.02), and marginally correlated with reduced BP_{ND} in the SN (ACTH; p=.10) and GP (cortisol; p=.07).
Conclusions: This proof-of-concept study suggests that CRF administration is associated with detectable changes in [^{11}C]-(+)-PHNO binding and can serve as a sensitive assay of dopamine release. Since addiction is associated with pathological stress and dopamine responses, this paradigm can help develop CRF antagonist strategies for treatment.

Keywords: corticotropin releasing factor, dopamine, positron emission tomography, [11C]-(+)-PHNO, stress-induced relapse

319. Decreased Thalamocortical Connectivity in Chronic Ketamine Users: Implications for Glutamatergic Mechanisms of Schizophrenia

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Background: Previous studies have revealed thalamic abnormalities in schizophrenia. Ketamine, a potent N-methyl-D-aspartate glutamate receptor antagonist, can mimic schizophrenia-like symptoms.
Methods: In this study, we addressed the thalamocortical connectivity in chronic ketamine users and healthy controls. 130 subjects (41 ketamine users and 89 control subjects) underwent resting-state functional MRI (fMRI). To investigate the specific functional relationships between the cortex and the thalamus, the cortex was partitioned into non-overlapping six regions of interest (ROI) (the prefrontal cortex, motor cortex/supplementary motor area, somatosensory cortex, temporal cortex, posterior parietal cortex, and occipital cortex). Mean BOLD time series were extracted for each ROI and entered into a seed-based functional connectivity analysis.
Results: Significantly less connectivity between the thalamus and the cortical ROI, including the prefrontal cortex, the motor cortex /supplementary motor area, and the posterior parietal cortex was observed in the ketamine use group. However, no increased thalamic connectivity was observed for the ketamine users as compared with control subjects. The functional connectivity between the posterior parietal area and the right lateral dorsal nucleus was significantly correlated to the individual ketamine craving score (p<0.05, corrected).
Conclusions: This study provides the first evidence of abnormal thalamocortical connectivity in chronic ketamine users. Our data further support a disruption model of the thalamocortical network and are consistent with a disconnection hypothesis of schizophre-

nia, and emphasize the functional importance of the thalamus in the pathophysiology of schizophrenia. Further understanding of glutamatergic mechanisms in schizophrenia may facilitate the evaluation of much-needed novel pharmacological agents for improved therapy of this complex disease.

Keywords: ketamine dependence, Thalamocortical circuitry, functional connectivity
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320. Impulsivity Following Deep Brain Stimulation (DBS) in the Ventral Capsule/Ventral Striatum (VC/VS) for Obsessive-Compulsive Disorder (OCD): A Case Series

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Background: Deep brain stimulation (DBS), an approved neurosurgical treatment for Parkinson's disease and essential tremor, has emerged as an investigational treatment for intractable psychiatric disorders, notably obsessive-compulsive disorder (OCD) and major depressive disorder. For treatment-refractory OCD, the Food and Drug Administration (FDA) has granted DBS a Humanitarian Device Exemption (HDE). Targeting the ventral capsule/ventral striatum (VC/VS), DBS for OCD has been associated with parameter-dependent, reversible mood effects, including smiling, laughter, and hypomania. Certain programming settings may also produce reversible increases in impulsivity. We report three cases of patients with OCD who experienced increased impulsivity following VC/VS DBS.
Methods: Three patients with treatment-refractory OCD underwent DBS implantation and programming under the FDA HDE. All available clinical data were reviewed. Obsessive-compulsive symptoms, adverse events, and medication therapies were noted.
Results: Three male patients (age 44-45 years, baseline Yale-Brown Obsessive Compulsive Scale [Y-BOCS]: 30-35) developed impulsivity during DBS treatment. Patient A's impulsivity occurred in the context of hypomania while Patient B's and C's were not associated with hypomanic symptoms. All patients experienced initial improvement in OCD symptoms (e.g., 20-71 % reduction in Y-BOCS score at 2 months), although Patient C eventually discontinued DBS due to loss of efficacy.
Conclusions: Impulsivity in the context of DBS for OCD highlights the need for clinical management guidelines and advances in DBS technology. Parameter changes and medications warrant consideration for the management of DBS-emergent impulsivity. Advances in DBS technology (e.g., remote monitoring/programming, multiple simultaneous targets, or responsive systems) may also mitigate risks of hypomania/impulsivity.

Keywords: OCD, Impulsivity, DBS, Adverse Effects, Safety

321. Attentional Bias to Symmetry and Cleaning Features in Obsessive-Compulsive Disorder: A Pilot Study

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Background: Bias in attention orienting towards threat stimuli is one of the most consistent mechanisms associated with anxiety disorders. Recently, the modification of attentional bias has shown to have therapeutic implications. The objective of this study is to investigate the presence of bias in attention orienting to symmetry and cleaning stimuli in adults with and without Obsessive Compulsive Disorder (OCD).
Methods: In this pilot study, attentional bias of 6 OCD patients and 6 healthy controls were evaluated in a referral OCD clinic at the University of Sao Paulo. Diagnostic assessment was performed using a structured psychiatric interview. Attentional bias was assessed using an innovative OCD-specific dot-probe task in which two pictures, one OCD-related (symmetry or cleaning features) and one neutral, were shown, followed by a small visual probe (120 trials). Attentional bias was measured using a subtraction of the reaction time from incongruent trials (where the probe replaced the neutral picture) from congruent trials (where the probe replaced the OCD-related picture). Wilcoxon test was performed to verify if the patient's median was higher than control's. Participants provided written informed consent.
Results: Attentional bias score for the symmetry stimuli was 17.58ms (SD=34.43) for patients and (-)0.37ms (SD=10.16) for controls (p=0.24). For the cleaning dimension, the attentional bias was 4.13ms (SD=35.26) and (-) 25.48ms (SD=33.18) for controls (p=0.08).
Conclusions: Our preliminary findings showed a trend to bias towards cleaning features among subjects with OCD. If replicated in larger samples, these results could have important implications for developing attentional bias modification training.

Keywords: obsessive-compulsive disorder, attentional bias
Supported by: FAPESP

322. Contribution of Balanced Dietary Proportions of N3- vs N6- Polyunsaturated Fatty Acids (PUFAs) in Ameliorating Post-Traumatic Stress (PTSD) Simulating Signatures

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Background: Our previously published transcriptomic study suggested potential benefits of fish oil on cerebral neurogenesis and neuroprotection, and contrasting therapeutic implications

to the neurodegenerative disorders. Here we explore potential for optimal dietary proportions of n3- vs. n6-PUFA to mitigate responses of mice manifesting PTSD-like behaviors. Diets with balanced proportions of the two PUFAs are suggested to have potential for preventing PTSD comorbidities such as cardiac diseases. Lower proportions of n6-PUFAs are associated with increased inflammation.:
Methods: Customized n-3 PUFA-enriched diet (ERD, n3:n6= 7:1), balanced diet (BLD, n3:n6= 1:1) and standard lab diet (STD, n3:n6= 1:6) were administered to three groups of C57BL/6J male mice from their weaning age until late adolescence. They were then used as either subjects or controls in an Aggressor-exposed stress (Agg-ES) model. A subject (C57BL/6J) was housed in a small mesh cage placed inside aggressor's (SJL) home-cage for 6h x 10d interrupted by brief and random direct pairing occurring 2-to-3 times/day. Controls had no Agg interaction. After 10d of Agg-ES, C57BL/6J's behavioral profiles were examined after either 1d or 4wk delay using a contextual cue paradigm (partition test). Hemibrains were then collected for transcriptomic analyses.
Results: Compared to STD, both ERD and BLD had elevated bodyweights and displayed stress reliance. ERD and BLD differed in eliciting certain behavioral endpoints, and displayed lesser plasticity effect after the 4w delay. Transcriptomic analysis suggested possible molecular factors contributing to the phenotypic outcome.
Conclusions: BRPUFA enriched diets showed potential to ameliorate PTSD like traits. Further analysis investigating drug-diet interaction would be productive.

Keywords: n-3 polyunsaturated fatty acids, n-6 PUFA, PTSD, mouse model, neutriogenomics
Supported by: US ARMY

323. Respiratory Sinus Arrhythmia (RSA), Executive Functioning, and a Mindfulness Intervention in Adolescent Males with Self-Regulation Disorders

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Background: Adolescents with learning disabilities (LDs) often present with comorbid self-regulation disorders. Integra Mindfulness Martial Arts [MMA] is a novel group treatment integrating mindfulness and cognitive behavioral therapy with martial arts training. While MMA has been shown to reduce externalizing behaviors and anxiety, we know little regarding its psychophysiological correlates. Respiratory sinus arrhythmia (RSA) is an index of heart rate variability that reflects individual differences in self-regulation. In adolescent males, antisocial and hostile behavior has been linked to lower levels of resting RSA.
Methods: Our sample included 19 adolescent males (12-15 years) with LDs and co-occurring self-regulation disorders enrolled in a 20-week MMA intervention (n=12) and waitlist controls (n=7). Resting RSA was indexed at 4 visits – pre, mid and post-intervention and at a 3 week follow-up, and the Behavior Rating Inventory of Executive Function self-report measure was collected.
Results: At pre-treatment, lower levels of resting RSA was related to an increased inability to 1) shift from one situation to another as circumstances demand (r=-.51, p<.03), 2) control emotional responses (r=-.56, p<.02), and 3) shift cognitive set and modulate emotions and behavior via inhibitory control (r=-.55, p<.02) across all participants. Mean levels of resting RSA increased from visit 1 to 4 in the treatment group only (p<.05).
Conclusions: Findings suggest lower RSA was related to poorer attentional flexibility, emotion regulation, and inhibitory control in this sample of adolescents with LD. MMA may positively influence autonomic adaptability, evidenced at the follow-up visit by higher resting RSA in the treatment group only.

Keywords: adolescent, males, autonomic nervous system, executive functioning, learning disabilities
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324. Brain Stimulation for Adolescent Depression

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Background: Repetitive transcranial magnetic stimulation (rTMS) is an emerging intervention for treatment resistant major depressive disorder (MDD) in adolescents. We investigated imaging biomarkers associated with treatment response. We hypothesized that lower baseline glutamate levels would predict beneficial rTMS treatment response and associate with lower MDD scores post-treatment.
Methods: Anatomical, resting state fMRI, and spectroscopy data were collected on a 3.0T GE MR750w. A 15-weekday rTMS treatment was applied targeting the left dorsolateral prefrontal cortex (DLPFC).
Results: No significant adverse events were reported. Clinical scores decreased with rTMS ($p < 0.001$). At baseline, responders had lower left DLPFC glutamate concentration ($p = 0.047$), which increased with rTMS compared to non-responders ($p = 0.01$) and correlated with the change in Hamilton depression rating scores (HAMD; $r = 0.58$, $p = 0.02$). Reduced DLPFC thickness was observed in responders ($p = 0.009$), and was also associated with greater change in HAMD ($r = -0.56$, $p = 0.03$). Lower left DLPFC cerebral blood flow at baseline was associated with greater change in Children's Depression Rating Scale ($r = -0.62$, $p = 0.02$) and Beck Depression Inventory scores ($r = -0.59$, $p = 0.03$). Finally, baseline resting state activity of the DLPFC inversely correlated with subgenual cortex activity in responders but not non-responders.
Conclusions: DLPFC glutamate, cortical thickness, and resting state connectivity may help identify both physiological mechanisms and clinical responsiveness in rTMS treatment of adolescent depression.

Keywords: Adolescence, Depression, Dorsolateral Prefrontal Cortex, Glutamate, Transcranial Magnetic Stimulation
Supported by: Children's Hospital Aid Society (CHAS)

325. A Pilot Study to Determine the Safety and Efficacy of H-Coil Transcranial Magnetic Stimulation (rTMS) in Treatment Resistant Anorexia Nervosa

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Background: There have been advances in understanding the neurobiology of Anorexia Nervosa (AN). Current research points to subcortical areas, such as insula as playing a role in the pathophysiology of AN. Up to this point, TMS has had functional capacity to stimulate only the superficial cortical regions of the brain. The new Hesed coil (Hcoil) was developed to activate deeper regions of the brain.
Methods: This non-blinded 12-week pilot study investigated safety and efficacy of H-coil deep rTMS treatment in patients with treatment resistant AN (TrAN). Patients underwent a series of tests, such as *lab tests*, *SCID, EDE*, *YBC-EDS*, *HRSD, MADRS*, *MOCA*, *BDI*, and *BAI* throughout the treatment. The primary end-points of the study were to assess (1) safety of rTMS as defined by the absence of adverse events, specifically seizures, and (2) efficacy, measured by clinical scales.
Results: Eight females diagnosed with trAN have completed baseline assessment. Most prevalent current co morbidities were GAD (62.5%), MDD (50%), and PD (12.5%). Out of eight participants four were enrolled and completed full trial. Four dropped out upon the completion of baseline assessment due to time commitment. No side effects reported. Next clinical outcomes were exhibited: decrease in HRSD and MADRS scores and in severity of obsessions and compulsions as measured by YBC-EDS.
Conclusions: Deep rTMS is a safe and well tolerated in patients with AN potentially resulting in improvement in mood and decrease in anxiety and obsessionality. This pilot study provides evidence to support proceeding with a larger RCT for rTMS in AN.

Keywords: transcranial magnetic stimulation, anorexia nervosa, pilot study, safety, efficacy

326. A Randomized Controlled Pilot Trial Suggesting that Cathodal Bi-frontal Transcranial Direct Current Stimulation (tDCS) May Shorten Sleep Onset Latency, and Increase Sleep Efficiency When Applied Before an Afternoon Nap.

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Background: Previous studies have demonstrated that a Bi-Frontal (F3/F4) negative direct current (DC) potential shift precedes sleep onset. Transcranial Direct Current Stimulation (tDCS) is a non-invasive form of brain stimulation capable of inducing DC potential shifts. We explored the effect of applying Anodal, Cathodal, or Sham tDCS prior to afternoon nap opportunities.
Methods: Ten healthy participants (Age 32.1±9.7SD, 7 women) each underwent three 30-minute afternoon naps with at least 48 hours between each nap opportunity. Immediately before each nap they received 10 minutes of (Anodal, Cathodal, or Sham) Bi-Frontal (F3/F4) tDCS at 2mA with return lead at the arm, delivered through saline soaked sponges (current density 0.057mA/cm2). Primary outcome measures included Sleep Onset Latency (SOL), and Sleep Efficiency (SE) as measured by Polysomnography (PSG).
Results: As we hypothesized, participants receiving Cathodal stimulation prior to a nap opportunity had a mathematical but not statistically significant reduction in SOL, and an increase in SE. SOL(Cathodal 9.6±8.2SD Mins; Anodal 11.8±11.3SD Mins; Sham 12.5±10.3SD Mins), SE (Cathodal 61.2%±27.8SD; Anodal 51.8%±34.1SD; Sham 46.8%±31.8SD). The results were confounded by a clear order effect (Participants had reduced SOL and increased SE on the third nap opportunity compared to the first or second.)
Conclusions: This preliminary evidence suggests that the use of Cathodal Bi-Frontal tDCS is feasible and safe and may increase sleep propensity in healthy participants during an afternoon nap, however further study with a larger sample is needed to definitively prove or disprove this hypothesis.
Clinicaltrials.gov registry #: NCT02176785

Keywords: Transcranial Direct Current Stimulation, Sleep, tDCS
Supported by: NIDA R25 DA020537-06, MUSC Department of Psychiatry Chairs Research Development Fund

327. The Effect of Bright Light Therapy for Improving Sleep Among Individuals with Mild Traumatic Brain Injury

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Background: Sleep problems, including excessive daytime sleepiness, are seen in about 50% of patients with mild Traumatic Brain Injuries (mTBI), and can negatively affect mood and cognitive performance. Since blue wavelength light has a strong influence on sleep patterns, melatonin suppression, and circadian rhythmicity, we hypothesized that 6-weeks of daily exposure to Morning Blue Light Therapy (MBLT) compared to an amber Sham Placebo Light Treatment (SPLT) would significantly improve daytime sleepiness from pre- to post-treatment.
Methods: Twenty-nine subjects (ages 18 -48), who experienced a mTBI in the past 18-months coupled with comorbid sleep difficulties, underwent a six-week light therapy using a bright light device every morning for 30 minutes. 14 subjects received MBLT and 12 subjects received SPLT. Participants also reported their daytime sleepiness using the Epworth Sleepiness Scale (ESS) before and after treatment. A mixed ANOVA was used to analyze ESS ratings between the two groups.
Results: There was a significant treatment x time interaction on ESS scores ($F(1,24)=4.485$, $p=0.04$). Post-hoc comparisons showed that, on average, individuals in the MBLT group showed

a 15.08% decrease in daytime sleepiness ratings on the ESS compared to a 4.26% increase for individuals in the SPLT group (p=.015).
Conclusions: The findings suggest that MBLT is an effective treatment for reducing post-concussion daytime sleepiness. Further work will be necessary to evaluate the effectiveness of MBLT on objective measures of sleep and sleepiness and the underlying neural mechanisms, as well as whether these changes are associated with improvements in cognitive functioning and emotional wellbeing.

Keywords: Mild Traumatic Brain Injury, Light Therapy, Sleep Disorders, Epworth Sleepiness Scale, Concussion
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328. Application Of Mindfulness-based Interventions In A Dual Diagnosis Patient

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Background: Relapse is a core feature of substance use disorders (SUD) that contributes significantly to the long-term functional impairment in patients with affective disorders.
Methods: In this case report and review of literature, we illustrate various challenges in treating treatment resistant depression (TRD) in a patient (Mr. B) with the high risk of relapse to opioids. In chronic stress, corticotrophin-releasing factor (CRF) are over sensitized and we portrait acute stress can cause unhealthy response to an over expressed CRF system. One treatment option to consider in preventing relapse was Mindfulness-Based Interventions (MBI).
Results: The case report is about the application of MBI in Mr. B to prevent relapse to opioid addiction. Mr. B benefited from MBI practices in several areas of his life and this can be explained with the help of an acronym FACES; Flexible (F): He became more cognitively flexible. Adaptive (A): He became more adaptive to changes at work, Coherent (C): He became more cognitively rational, Energized (E): He demonstrated more energy to make connection with his extended family, Stable (S): He became far more emotionally stable.
Conclusions: In summary, the stressors of Mr. B might have mobilized CRF system to activate HPA, and extra-hypothalamic actions of CRF can stimulate the neuronal circuits responsible for stress-induced anxiety, dysphoria, and reinstatement of drug abuse behaviors. As hypothesized, practicing MBI was associated with abstinence from substance use, increased mindfulness, acceptance of mental health issues and remission of psychiatric symptoms.

Keywords: Opioid Use Disorder, corticotrophin-releasing factor, Mindfulness Meditation, Chronic Stress, Treatment Resistant Depression

329. To Crave or Not to Crave: Individual Variability in Alcohol Craving Is Associated with the Efficacy of TMS as a Treatment Tool for Alcoholism

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Background: Background. Cue-elicited craving is one of the biggest factors contributing to chronic alcohol use and relapse among alcoholics. Current pharmacological options for treatment-seeking alcoholics do not directly target medial prefrontal-striatal circuits involved in craving. The purpose of this study was to determine whether continuous theta burst stimulation (cTBS) to the medial prefrontal cortex (mPFC) could 1) decrease baseline functional activity and connectivity with the medial prefrontal cortex and 2) decrease alcohol cue-evoked BOLD signal in the mPFC and striatum.
Methods: In this single blind, sham-controlled, crossover study 17 alcohol-dependent individuals received cTBS (real or sham) to the left frontal pole/mPFC (EEG: FP1) (2 trials of 1800 pulses, 60 sec intertrain interval). The baseline functional activity and connectivity with the mPFC as well as alcohol cue-evoked BOLD signal were measured immediately before and after the cTBS session using interleaved TMS/BOLD and standard BOLD imaging respectively. Self-reported craving was collected throughout each visit.
Results: A single session of cTBS decreased baseline mPFC BOLD signal as well as cue-evoked BOLD signal in the mPFC. There was no consistent effect of real versus sham TMS on craving scores however, which may be related to individual variability in cue-evoked craving.
Conclusions: These preliminary data suggest that it is possible to decrease activity in limbic circuitry involved in alcohol craving, but the efficacy of cTBS as a tool may be related to individual variability in cue-reactivity. A larger sample size will allow us to investigate the role of demographic and alcohol use variables related to the efficacy of TMS as a novel treatment for addiction.

Keywords: brain stimulation, addiction, neuroimaging, craving, theta burst
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330. Fear Conditioning in Obsessive-compulsive Disorder Patients Treated with Sertraline: Preliminary Results

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Background: Milad et al. (2013) found that medicated obsessive-compulsive disorder (OCD) patients presented worse fear extinction recall, characterized by low extinction retention index (ERI), than healthy subjects, and that the severity of OCD was inversely correlated with the ERI. Our aim was to replicate these findings in a drug-free sample and investigate the short-term effects of medication over extinction recall.
Methods: Fifteen drug-free adult OCD patients (10 female, 5 male; mean age=38.3, SD=13.4) with current symptoms of at least moderate severity, and 14 healthy subjects (8 female, 6 male; mean age=36.9, SD=15.3) were evaluated with the fear conditioning protocol developed by Milad et al. (2003). After 4 weeks of treatment with sertraline up to 200 mg/day, OCD patients were retested with the fear conditioning protocol with a different order of stimuli.
Results: Forty-six percent of patients and 36% of controls were able to discriminate between conditioned and not-conditioned stimuli at baseline (chi-square, p=0.581). Post-treatment, 63% of patients discriminated between stimuli (chi-square, p=0465). Patients (mean ERI=58%, SD=0.4) did not differ from healthy subjects (mean ERI=59%, SD=0.3) regarding ERI at baseline (t-test, p=0.988). OCD severity did not correlate with ERI (Spearman's rho=0.212, p=0.487). Eight OCD patients underwent treatment and did not present a significant improvement of ERI (post-treatment ERI=67%, SD=0.3; paired t-test, p=0.750).
Conclusions: In drug-free OCD patients, we did not replicate previous findings of an association between failure to recall extinction and OCD diagnosis or symptom severity. However, low conditioning and our small sample size may account for our negative results.

Keywords: obsessive-compulsive disorder, fear conditioning, sertraline
Supported by: Fundação de Amparo à Pesquisa do estado de São Paulo

331. Effects of Ketamine on Suicidal Ideation in Patients with Mood and Anxiety Disorders: A Prospective, Randomized Controlled Pilot Study

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Background: Suicide is a devastating public health problem with paucity of available treatments. We have previously shown that a single intravenous (IV) of ketamine, a glutamate N-methyl-d-aspartate(NMDA) receptor antagonist, is associated with a rapid reduction in depressive symptoms in patients with treatment resistant major depression(TRD). This study was designed to investigate whether ketamine, compared to a control condition, could decrease the severity of the suicidal thinking across psychiatric diagnoses in patients with high levels of suicidal ideation (SI)
Methods: We conducted a double blind, randomized, controlled, pilot study of ketamine in inpatients and outpatients with clinically significant SI (4 or more on the SI item of Montgomery Asberg Depression Rating Scale,MADRS-SI). Patients received a single IV infusion of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) in addition to standard of care. Suicidal ideation measured using the Beck Scale for Suicidal Ideation (BSS) 24 hours post-treatment represented the primary outcome. Secondary analyses included MADRS-SI score at 24 hours and additional measures beyond the 24-hour time point.
Results: Twenty four patients (10 inpatient, 14 outpatient) were randomized to receive ketamine or midazolam in a 1:1 scheme. BSS score was not different between the treatment groups at 24 hours (p=0.32), however a significant difference emerged at 48 hours (p=0.047). The treatment effect was no longer significant at 72 hours or 7 days. MADRS-SI score was lower in the ketamine compared to midazolam group at 24 hours (p=0.05).
Conclusions: The findings of current study provide initial support for the safety, tolerability and preliminary efficacy of ketamine as an intervention for suicidal ideation in patients who are at elevated risk for suicidal behavior.

Keywords: Suicidal ideation, Ketamine
Supported by: American Foundation for Suicide Prevention (AFSP)

332. First Tear Comparison of 3 New Antidepressants

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Background: This study examines the effectiveness and tolerability of 3 newly available antidepressants in depressed outpatients.
Methods: A retrospective chart review was performed on all patients being seen in an outpatient psychiatric clinic. Data collected included demographics, medication history, and the results of the PHQ-9 depression screening given at each visit.

Patients were included in the study if they were diagnosed with a mood disorder and were prescribed levomilnacipran, vilazodone, or vortioxetine in the first year that they were commercially available.
Results: 27 patients were prescribed levomilnacipran (41% who were diagnosed bipolar), 20 patients were prescribed vilazodone (20% bipolar), and 45 were prescribed vortioxetine (20% bipolar) during their first year of availability. 29% of levomilnacipran patients stopped treatment with it in the first month, compared to 25% for vilazodone and 23% for vortioxetine. Patients were on these medications for an average of 4.2 months (±2.1). PHQ-9 scores for patients on levomilnacipran improved from 16.5 to 15.8, patients on vilazodone from 12.4 to 10, and patients on vortioxetine from 18.4 to 12.2 (p<.002).
Conclusions: All 3 medications showed similar rates of tolerability and side effects. While all 3 medications showed improvements in depression scores, vortioxetine was the only one to show significant improvement, while levomilnacipran was used in a sample with a higher rate of bipolar disorder.

Keywords: Depression, Levomilnacipran, Vilazodone, Vortioxetine

333. Antisuicidal Response after Ketamine Infusion Is Associated with Reduced Wakefulness in Treatment Resistant Depression

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Background: Disrupted sleep has been associated with an increased risk of suicide. Previous studies have investigated how psychotropic medications impact sleep and whether there is an association between sleep changes and clinical response. However, no studies have investigated such a relationship with the antisuicidal effect of ketamine. The aim of this study was to evaluate how ketamine impacts wakefulness using polysomnography and to determine how sleep after ketamine was different in those who have an antisuicidal response compared to those who do not.
Methods: 34 participants diagnosed with major depression or bipolar depression who had suicidal ideation at baseline completed polysomnography the night before and the night after a single ketamine infusion, which was administered at 0.5 mg/kg over 40 minutes. A generalized linear mixed model evaluated differences in wakefulness between those who had an antisuicidal response to ketamine and those who did not, while controlling for baseline sleep time.
Results: There was a significant difference in wakefulness on the night after ketamine infusion between those participants who demonstrated a suicidal versus non-suicidal response when controlling for baseline sleep (p=0.035). Using healthy controls as a comparison group, there was not a significant difference between the sleep of those with an antisuicidal response after ketamine and the healthy controls (p=0.78).
Conclusions: Participants with an antisuicidal response to ketamine showed significant improvement in disrupted sleep, even when controlling for baseline sleep. Reductions in time awake following ketamine may point to an underlying biological mechanism for ketamine's effect on suicidal ideation.

Keywords: Ketamine, Suicide, Sleep, Treatment-Resistant Depression
Supported by: Intramural Research Program, NIH

334. Lithium and Valproate Levels Do Not Correlate with Ketamine's Antidepressant Efficacy in Treatment-Resistant Bipolar Depression

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Background: Among other effects, ketamine and lithium are both inhibitors of glycogen synthase kinase 3 and, at individually subeffective doses in rodents, lithium and ketamine had synergistic antidepressant-like effects. We therefore hypothesized that ketamine's antidepressant effect is improved with therapeutic-dose lithium vs. valproate and serum lithium levels positively correlate with ketamine's antidepressant efficacy.
Methods: 36 treatment-resistant bipolar depressed patients maintained on therapeutic-dose lithium (n=23, 0.79±0.15 mEq/L) and valproate (n=13, 79.6±12.4 µg/mL) received 0.5mg/kg ketamine infusion in a randomized, double blind, placebo-controlled crossover trial. The primary depression outcome measure, the Montgomery Åsberg Depression Rating Scale (MADRS), was assessed pre-infusion and at numerous post-infusion time points. A linear mixed model assessed medication group differences in MADRS, and bivariate correlations were performed with same-day pre-ketamine infusion lithium and valproate levels with percent change in MADRS from baseline to 230 min, day one and day seven post-infusion.
Results: There was a significant improvement in depression on lithium (F1, 118=152.08, p<.001, d=2.27) and valproate (F1, 128=20.12, p<.001, d=0.79), but there was no statistically significant difference between mood stabilizer groups (F1,28=2.51, p=.12, d=0.60). Serum lithium and valproate levels did not correlate with ketamine's antidepressant efficacy.
Conclusions: Although potentially underpowered, lithium may not potentiate ketamine's antidepressant efficacy in treatment-resistant bipolar depression.

Keywords: ketamine, bipolar disorder, lithium, valproate, treatment-resistant depression
Supported by: NIH-NIMH-IRP

335. Association of Obesity and Levels of Inflammatory Markers on Treatment Outcome with Adjunctive (6S)-5-methyl-5,6,7,8-tetrahydropteroyl-L-glutamic Acid (CH3-FH4) in MDD Patients Who are Inadequate Responders to SSRIs

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Background: Adjunctive treatment with (6S)-5-methyl-5,6,7,8-tetrahydropteroyl-L-glutamic acid (CH3-FH4, Deplin®) significantly improved treatment outcomes in patients with major depressive disorder (MDD) and an inadequate response to antidepressants. This exploratory analysis evaluated baseline levels of specific cytokines, CRP, leptin, adiponectin, and body mass index (BMI) on CH3-FH4 treatment response.
Methods: Adults with MDD and an inadequate response to an antidepressant were eligible. Patients were randomized according to the Sequential Parallel Comparison Design (SPCD) to Placebo-Placebo, Placebo- CH3-FH4 (15 mg/day) or CH3-FH4 (15 mg/day) during two 30-day phases. Treatment effect was estimated from baseline concentrations of individual biomarkers (IL-1α, -1β, IL-2, -4, -5, -6, -8, -10, -12 (p70), -13, and -17, TNFα, and IFNγ, leptin, adiponectin), BMI, and combinations. The effects of individual biomarkers above and below the median were assessed.
Results: Change in HAMD-28 from baseline was greater with CH3-FH4 vs. Placebo (pooled treatment effect -2.74, 95% CI -4.99, -0.48, p=0.017) overall and for those with baseline BMI ≥30 kg/m2 (pooled treatment effect -4.6, 95% CI -7.22, -1.98, p=0.001), but not BMI <30. Pooled mean differences for baseline levels of individual markers above median were significant (CH3-FH4 vs. Placebo) for TNFα, IL-8, CRP, and leptin and for combinations of BMI ≥30 kg/m2 with elevated levels of TNFα, IL-6, IL-8, CRP, and leptin (pooled treatment effect -6.31 to -3.98 [p≤0.05]).
Conclusions: Inflammatory and obesity-related factors were associated with greater symptom improvement with CH3-FH4. Combinations of BMI ≥30 kg/m2 and specific factors predicted improved response to CH3-FH4 in MDD patients with an inadequate antidepressant response.

Keywords: Depression, Nonresponders, (6S)-5-methyl-5,6,7,8-tetrahydropteroyl-L-glutamic, Inflammation, Treatment
Supported by: Pamlab, Inc.

336. Subclinical Vascular Impairment and Elevated Levels of Oxidative Stress and Inflammation Among Adolescents with Bipolar Disorder

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Background: Bipolar disorder (BD) is characterized by substantial burden of hypo/manic and depressive symptoms and by premature and excessive mortality from cardiovascular disease (CVD). Characterizing biomarkers of BD is pertinent to understanding the increased CVD risk and disease progression. Inflammation and oxidative stress are key potential biomarkers.
Methods: 60 adolescents (13-19 years old), with no CVD (40 adolescents with BD, and 20 controls) were recruited. Diagnoses were determined using semi-structured interviews (K-SADS-Present and Lifetime Version). Standard procedures were used for ultrasound measurements of carotid intima media thickness (cIMT) and flow-mediated dilation (FMD). Serum levels of inflammation and oxidative stress were determined using ELISA. Non-parametric analyses (Kruskal-Wallis and Mann-Whitney U tests) were performed using SPSS 22.
Results: cIMT and FMD were not significantly different between groups. Lipid hydroperoxides ($mean_{controls}$= 6.4, SD= 3.6, $mean_{BD}$= 10.5, SD=4.9; $\chi^2(3)$= 8.8, p=.03) , Interleukin (IL) 1-alpha ($mean_{controls}$=247.2, SD=175.3, $mean_{BD}$= 463.1, SD=253.9; $\chi^2(3)$= 10.1, p=.018) and IL-6 ($mean_{controls}$= 4.9, SD= 6.4, $mean_{BD}$= 8.9, SD=7.7; $\chi^2(3)$= 15.1, p=.002), but not 4-hydroxynonenal, were significantly greater in the BD group compared to controls. Notably, lipid hydroperoxides are greater in BD I than BDII, which are both greater than BDNOS and controls ($\chi^2(3)$= 8.8, p = .03).
Conclusions: Adolescents with BD have significantly greater levels of oxidative stress and inflammation, compared to healthy controls. Oxidative stress and inflammation should be investigated further as biomarkers of BD, which may sub-serve the BD-CVD link.

Keywords: oxidative stress, inflammation, adolescent, bipolar disorder, vascular impairment
Supported by: Heart and Stroke Foundation (Ontario) NA7231

337. Differential Associations Between Inflammation and Cognition Based on BDNF Levels in Adolescent Bipolar Disorder

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Background: Inflammation and BDNF have been implicated in bipolar disorder (BD) pathophysiology. Similarly, cognitive dys-

function, particularly in frontal-executive tasks, is evident within and between mood episodes in BD. C-reactive protein (CRP) is correlated with set-shifting performance in BD adults and adolescents. However, no study has examined the impact of BDNF on this association.
Methods: CRP and BDNF levels were measured in 30 BD adolescents and 25 control participants. Cognition was assessed using the Intra-Extra Dimensional (IED) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). A median-split divided participants based on BDNF levels. T-tests or Mann-Whitney U-tests were used for between-group comparisons, and Spearman correlations to compare CRP and cognition.
Results: CRP and BDNF were not significantly different between groups. Within the low BDNF sub-group, CRP was significantly negatively correlated with IED omnibus Z-scores in BD (ρ=-0.630, p=0.002) and the whole-sample (ρ=-0.650, p=0.044). CRP was significantly negatively correlated with 5/7 IED sub-scores in the whole-sample and 3/7 in BD participants; the whole-sample results, but not BD, survived multiple-comparison correction. In controls, no correlations were seen in the low BDNF subgroup. The high BDNF subgroup had no significant correlations.
Conclusions: CRP may negatively modulate set-shifting deficits in BD, and BDNF may mitigate this effect. Further studies involving larger sample sizes and repeated-measures, longitudinal study designs are warranted to better understand the direction of the observed associations. Studies of anti-inflammatory therapeutic approaches are warranted to examine whether these approaches ameliorate cognitive dysfunction, particularly among BD adolescents with low BDNF.

Keywords: Bipolar Disorder, Inflammation, BDNF, Cognition
Supported by: NARSAD/Brain and Behaviour Research Foundation

338. A Double-Blind Placebo-Controlled Study of Exenatide for the Treatment of Weight Gain Associated with Olanzapine in Overweight or Obese Adults with Bipolar Disorder, Major Depressive Disorder, Schizophrenia or Schizoaffective Disorder

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Background: Second generation antipsychotics are often associated with weight gain. Specifically, olanzapine has been associated with significant weight gain as well as glucose dysregulation. Exenatide is used as adjunctive therapy in adults with type 2 diabetes and has been associated with reduced food intake and weight loss. Exenatide may be effective in reducing appetite and may in turn lead to changes in weight and BMI.
Methods: Sixty adults with major mood or psychotic disorders (ages 18-55 years) were randomized to treatment with exenatide or placebo (5-10mcg) in combination with olanzapine for 16 weeks. Subjects required a weight increase of ≥7% of their body weight while taking olanzapine or be currently overweight/obese to participate. Patients were on a stable of olanzapine for one month (four weeks) and not meet criteria for a current mood or psychotic episode.
Results: Weight and BMI change in the exenatide group were also significantly less than the placebo group (exenatide-placebo, weight-change difference = -7.9 lbs, p=0.02; BMI-change difference = -1.3 kg/m2, p=0.02).
Conclusions: Exenatide may be effective in stabilizing and ultimately preventing the trend of weight gain associated with olanzapine. Future studies may look at the addition of exenatide as an early intervention for olanzapine-induced weight gain or be used in conjunction with olanzapine when it is first initiated to promote weight stability and prevent weight gain.

Keywords: Bipolar Disorder, Metabolic, Weight Gain, Exenatide, Olanzapine

339. Repeated Treatments of Electroconvulsive Seizure Activates AMPK and Inhibits mTOR Signal Pathways in Rat Frontal Cortex

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Background: AMP-activated protein kinase (AMPK) plays a critical role in maintaining metabolic homeostasis, and its signaling in the brain is implicated in multiple aspects of brain development and function. AMPK can interact with mammalian target of rapamycin (mTOR) signal pathway, which plays crucial role in protein translation. In this study, the effects of repeated electroconvulsive seizure (ECS), a model for electroconvulsive therapy (ECT), on AMPK-related signal pathways were investigated in rat frontal cortex.
Methods: We have examined the effects of repeated ECSs on the phosphorylation of AMPK and TOR-related molecules and related changes in expression of autophagy genes in the rat frontal cortex.
Results: Repeated treatments of ECS for 10 days (E10X) increased the phosphorylation of AMPKα (Thr172) in frontal cortex neurons. Activation of AMPK signal pathway by E10X was also evidenced by increased phosphorylation of its up-streams, LKB1, CaMK4, and TAK1, and substrates, ACC and HMG-CoA reductase. Ulk1 is another substrate of AMPK, which is involved in autophagy induction when accompanied with of mTOR inactivation. Wide distribution of Ulk1 immunoreactivity in neurons of frontal cortex was demonstrated. E10X increased AMPK-responsible phosphorylation of Ulk1 (Ser317, Ser555) and binding of AMPK to Ulk1 and 14-3-3. Phosphorylation of raptor at Ser792 was increased by E10X, which is known to inhibit mTOR by AMPK. Actually, phosphorylation of mTOR, p70S6K, and S6, and protein translation activity were reduced by E10X, indicating the suppression of mTOR activity in frontal cortex. In this condition, protein and mRNA level of LC3 and Atg5 conjugation were increased, markers of autophagy.
Conclusions: Repeated ECS treatments activate AMPK-Ulk1 pathway and inhibit mTOR pathway, which could induce autophagy in frontal cortex.

Keywords: electroconvulsive therapy, AMPK, mTOR, Ulk1, autophagy
Supported by: Korea Healthcare Technology R&D Project, Ministry for Health & Welfare (HI12C1470)

340. Effect of Etanercept, a TNF-α Inhibitor, on Depressive-Like Behavior in Cafeteria Diet-Fed Rats

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Background: Obesity has been shown to be associated with depression. Recent studies have reported that obesity is not only as a metabolic disorder but also as an inflammatory disease. In this study we explored the effect of etanercept, a TNF-α inhibitor, on depressive-like behavior in cafeteria diet (CD)-fed rats.
Methods: Six-week-old male Wistar Albino rats (300-350 g) were divided into three groups (n=10): Control (not exposed to CD), CD-fed (exposed to CD during 5 weeks) and CD-fed+etanercept (exposed to CD and treated with etanercept (0.8 mg/kg/weekly/subcutaneously during 5 weeks). CD was used to generate diet-induced obesity. The body weights of animals were measured weekly. Forced swimming test (FST), the sucrose consumption and preference test were used to investigate antidepressant effect of etanercept. One-way ANOVA and Tukey's post hoc test used for statistical analysis.
Results: After 5 weeks, the body weight of CD-fed group was higher than control group ($p<0.001$) and CD-fed+etanercept group was lower than CD-fed group ($p<0.05$). In FST, there were differences between three groups in terms of immobility time during second day of testing ($F(2,27)=8.174$, $p=0.017$). CD-fed group exhibited more immobility than control group ($p<0.01$), while there was no difference between control and CD-fed+etanercept group ($p>0.05$). Sucrose consumption and sucrose preference in CD-fed group was lower than control group ($p<0.05$). However, the behavior of rats in CD-fed+etanercept group did not differ from the control group ($p>0.05$).
Conclusions: The results indicate the antidepressant effect of etanercept on diet-induced obesity and TNF-α may play crucial role on obesity-related mechanisms.

Keywords: obesity, depression, TNF-α, cafeteria diet, rats

341. Vortioxetine Disinhibits Pyramidal Cells by Blocking Serotonin Excitation of GABAergic Interneurons in the Hippocampus

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Background: The novel antidepressant vortioxetine is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and serotonin (5-HT) transporter inhibitor. We have previously shown that vortioxetine disinhibits pyramidal cell function and enhances synaptic plasticity in the rat hippocampus (Dale et al., 2014 *J Psychopharmacol* 28(10):891-902). Here we investigate the mechanisms by which vortioxetine mediates these effects by studying the effect of vortioxetine on the activity of gamma-butyric acid (GABA) interneurons in rat hippocampal brain slices.
Methods: Patch clamp recordings were performed in hippocampal slices from CA1 striatum radiatum interneurons. 5-HT and the 5-HT_3 receptor agonist m-CPBG were applied locally to the brain slices due to fast desensitization of their responses. All other compounds were added to the extracellular buffer.
Results: Application of 5-HT produced an inward current that depolarized GABAergic interneurons and in some cases elicited action potential firing. Vortioxetine and the selective 5-HT_3 receptor antagonist ondansetron attenuated the 5-HT response. Furthermore, the 5-HT_3 receptor agonist m-CPBG depolarized GABAergic interneurons in ~75% of recorded cells. Pretreatment with vortioxetine or ondansetron blocked the m-CPBG effect.
Conclusions: Activation of 5-HT_3 receptors leads to depolarization of GABAergic interneurons located in the striatum radiatum area of the hippocampus. Vortioxetine blocks this effect by antagonizing 5-HT_3 receptors. Inhibition of interneurons leads to enhanced pyramidal cell function. Given the central role of the hippocampus in cognition, and the key role that pyramidal cells play in hippocampal output, these findings suggest a cellular correlate to the observed effects of vortioxetine on cognition.

Keywords: serotonin, antidepressant, vortioxetine, hippocampus, electrophysiology

342. Effects of Antidepressants in a Rat Model of Co-morbid Cognitive Deficits and Depression-like Behavior Induced by Ovariectomy

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Background: Ovariectomy (OVX) is associated with spatial memory deficits and depression-like behavior in rodents as is menopause in human. However, the effects of antidepressants with different mechanism of action have not been systematically studied in this animal model. Therefore, we measured the effects of chronic fluoxetine (selective serotonin reuptake inhibitor, SSRI), duloxetine (serotonin-norepinephrine reuptake inhibitor, SNRI), vilazodone (serotonin reuptake inhibitor and 5-HT1A receptor partial agonist) and vortioxetine (5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of serotonin reuptake).
Methods: Adult female Sprague-Dawley rats underwent ovariectomy and received at least 4 weeks of treatment via food (15 to 32 rats per group): control, vortioxetine, fluoxetine, duloxetine or vilazodone. Animals were tested in the novel object placement test (for visuospatial memory) and forced swim test (for depression-like behavior). Gonadally intact female rats were included as controls. Drug exposure was confirmed with ex vivo SERT occupancy analysis. ANOVA followed by post-hoc protected test was used for data analysis and $p<0.05$ was considered significant.
Results: OVX induced deficits in visuospatial memory and increased immobility in the forced swim test. In OVX rats, chronic vortioxetine improved visuospatial memory and reduced depression-like behavior, neither chronic duloxetine chronic vilazodone nor chronic fluoxetine significantly changed performance in any of the tests. All drugs doses fully occupied the serotonin transporters.
Conclusions: Ovariectomy induced visuospatial memory deficits and increased depression-like behavior, consistent with co-morbid

mood and cognitive deficits during menopause. Vortioxetine both reversed memory deficits and reduced depression-like behavior in OVX rats.

Keywords: vortioxetine, forced swim test, visuospatial memory, SSRI (selective serotonin reuptake inhibitor), SNRI (serotonin-norepinephrin reuptake inhibitor)
Supported by: H. Lundbeck A/S

343. Vortioxetine Selectively Modulates Synaptic vs Extrasynaptic Glutamate Neurotransmission

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Background: Vortioxetine is a multimodal acting antidepressant that may have beneficial effects on some aspects of cognitive function. Although vortioxetine's pharmacological effects are mediated via serotonergic mechanisms, recent work suggests that these serotonergic actions indirectly modulate glutamate neurotransmission in a manner that is relevant for cognitive function. This poster reviews key data suggesting that vortioxetine selectively increases synaptic glutamate neurotransmission without affecting extrasynaptic glutamate signaling and reverses cognitive deficits induced by glutamate dysregulation.
Methods: Vortioxetine's effects on long-term potentiation (LTP), 5-HT-mediated inhibitory postsynaptic currents (IPSCs) in hippocampal pyramidal neurons, cortical pyramidal neuron firing rates, frontal cortical oscillatory power, and cortical and hippocampal extracellular glutamate concentrations were investigated using slice electrophysiology, in vivo single unit recording, electroencephalography, and microdialysis, respectively. Vortioxetine's ability to reverse glutamate-related cognitive dysfunction was investigated using models including MK-801-induced social recognition memory deficits and subchronic PCP-induced attentional set shifting impairments.
Results: Vortioxetine significantly enhanced LTP, reduced the frequency and amplitude of 5-HT-mediated IPSCs in hippocampal pyramidal cells, increased the firing rate of cortical pyramidal neurons [1], and enhanced gamma oscillatory power, but had no effect on cortical or hippocampal extracellular glutamate concentrations. Furthermore, vortioxetine reversed MK-801-induced social recognition memory deficits and subchronic PCP-induced impairments in attentional set shifting.
Conclusions: Taken together, these data suggest that vortioxetine selectively increases synaptic glutamate neurotransmission in a manner that is relevant to cognitive function without altering extrasynaptic glutamate signaling.

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Keywords: Major Depressive Disorder, Vortioxetine, Lu AA21004, glutamate

344. Chronic Vortioxetine Treatment Improves Pattern Separation in Mice

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Background: Pattern separation (PS), a neurogenesis-dependent task, is a process that transforms similar events into discrete, non-overlapping representations. Pro-neurogenic compounds may therefore have therapeutic potential for patients displaying PS deficits, e.g., individuals with anxiety disorders. Since the multimodal antidepressant vortioxetine increases neurogenesis in mice, this study investigated the effects of vortioxetine treatment on the performance of adult and aged mice in the PS paradigm.
Methods: Adult (8 weeks old) and aged mice (18 months old) were treated with vortioxetine (1.8 g/kg chow, 4 weeks) before PS performance assessment. In the PS paradigm, mice were trained to discriminate between an aversive shock-associated training context (A) and a similar non-aversive (no-shock) context (B). Measurement of freezing levels in both contexts allowed assessment of discrimination between the two contexts. The effects of age and vortioxetine treatment on hippocampal neurogenesis were also assessed.
Results: Vortioxetine-treated mice exhibited significantly lower levels of freezing behavior in context (B) relative to context A four days earlier than controls. In contrast, age significantly impaired PS performance. Vortioxetine's effects on PS in aged mice were confounded by an anxiolytic-like effect since freezing behaviour was reduced in both contexts.
Conclusions: This is the first study showing that chronic vortioxetine treatment improves PS performance in adult mice suggesting a pro-cognitive effect in this paradigm. Age significantly impaired PS and chronic treatment with vortioxetine decreased freezing activity, suggesting that anxiolytic-like effects may be implicated in vortioxetine's effects in aged mice. Ongoing studies are evaluating the relationship between adult hippocampal neurogenesis and PS.

Keywords: Pattern Separation, Antidepressant, Ageing, Neurogenesis, Mice
Supported by: Lundbeck Research USA, Inc.

345. The 5-HT2A/1A Agonist Psilocybin Enhances Empathy and Reduces Social Pain in Healthy Volunteers

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Background: Social cognition is a crucial factor influencing development, progress, and treatment of psychiatric disorders. Particularly, depressed patients show an increased negative reaction to social exclusion and deficits in empathy. The 5-HT2A/1A receptor agonist psilocybin has been reported to reduce the neural response to negative stimuli. However, it is not known if

this extends to negative social interaction and whether 5-HT2A/1A receptor stimulation affects empathy. Given the clear need for improved treatment of socio-cognitive functioning in psychiatric disorders, it is important to better understand the neuronal and neuromodulatory substrates of social cognition.
Methods: This study assessed the neural response to ostracism after the acute administration of psilocybin (0.215mg/kg) and placebo in 21 healthy volunteers using functional magnetic resonance imaging. Furthermore, we assessed cognitive and emotional empathy using the Multifaceted Empathy Test. A double-blind, randomized, cross-over design was applied with volunteers counterbalanced to receive psilocybin and placebo in two sessions at least 10 days apart.
Results: The neural response to social exclusion was reduced in the dorsal anterior cingulated cortex (peak: x=6,y=26,z=22,p<0.05,FWE) after psilocybin administration versus placebo. Emotional empathy was increased after psilocybin administration (F(1,31)=7.09,p0.27).
Conclusions: These results indicate that the 5-HT2A/1A receptor subtypes play an important role in the modulation of socio-cognitive functioning and therefore may be relevant for the treatment of social cognition deficits in psychiatric disorders. In particular, they may be important for the normalization of empathy deficits and increased negative reaction to social exclusion in depressed patients.

Keywords: serotonin, social cognition, imaging, psilocybin, fMRI

346. Development of Animal Models of the Effort-related Motivational Symptoms of Depression (i.e. with a Focus on Drug Development)

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Background: Organisms frequently make effort-related decisions based upon assessments of motivational value and response costs. Considerable evidence indicates that nucleus accumbens dopamine (DA) and related forebrain circuits are involved in regulating behavioral activation and effort-related processes.
Methods: Various pharmacological and neurochemical conditions can cause animals to reallocate their instrumental behavior away from food-reinforced tasks with high response costs, and instead select less effortful food-seeking behaviors. It has been suggested that tasks that assess effort-based decision making in rodents could be used as models for the effort-related motivational symptoms seen in people with depression, schizophrenia and other disorders. Recent studies have investigated the effects of various conditions associated with motivational symptoms across multiple disorders (e.g. stress, proinflammatory cytokines, catecholamine depletion) on effort-related decision making in rats. For example, tetrabenazine inhibits vesicular monoamine transporter-2 (VMAT2), and has been shown to induce or exacerbate depressive symptoms humans.
Results: Administration of tetrabenazine at doses that reduce accumbens DA levels and affect DA-related signal transduction (i.e. DARPP-32 expression) alters effort-related decision making in rats responding on several different behavioral tasks, biasing animals towards low-effort alternatives. These effects of tetrabenazine on effort-related choice behavior can be reversed by co-administration of the adenosine A2A antagonist MSX-3, the nutritional supplement curcumin, the MAO-B inhibitor deprenyl, and the well characterized antidepressant bupropion.
Conclusions: These studies are consistent with the NIMH RDoC (Research Domain Criteria) approach for modeling symptoms and circuits related to psychopathology, and could be useful for the development of drug treatments for effort-related motivational symptoms in humans.

Keywords: depression, motivation, anergia fatigue, dopamine, animal models
Supported by: NIMH, University of Connecitut Research Foundation

347. Brexpiprazole Alters the Activity of Monoaminergic Systems Following Subacute and Long-term Administration: An in vivo Electrophysiological Study

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Background: Brexpiprazole (OCP-34721) is a chemical agent currently under investigation for add-on treatment of depression and for schizophrenia. In our previous *in vivo* study where brexpiprazole was administered acutely (Oosterhof et al. 2014), we demonstrated agonistic action of brexpiprazole on serotonin $(5\text{-HT})_{1A}$ receptors, partial agonism at dopamine D_2 receptors, and antagonistic at 5-HT_{2A} and α_2-adrenergic heteroceptors. To complement these findings, we assessed the effect of subchronic and long-term brexpiprazole administration on monoaminergic systems.
Methods: Brexpiprazole (1 mg/kg, subcutaneous) or vehicle was administered once daily for 2 or 14 days. Single-unit electrophysiological recordings from noradrenergic neurons in the locus coeruleus (LC), serotonergic neurons in the dorsal raphe nucleus (DRN), dopaminergic neurons in the ventral tegmental area (VTA), and pyramidal neurons in the CA3 region of the hippocampus were obtained in adult male Sprague-Dawley rats under chloral hydrate anesthesia.
Results: Brexpiprazole increased the firing rate and burst activity of LC noradrenergic neurons. Furthermore, it increased NE tone on α_2- but not α_1-adrenergic receptors in the hippocampus. Administration of two, but not 14 days of brexpiprazole increased the firing rate of 5-HT neurons in the DRN. Despite this latter result, blockade of 5-HT_{1A} receptors had a strong disinhibiting effect on pyramidal neurons in the hippocampus after 14 days of brexpiprazole administration. In the VTA, firing parameters remained unchanged.
Conclusions: Sustained brexpiprazole administration enhanced serotonergic and noradrenergic tone in the hippocampus, while it had no effect on VTA dopamine neurons. Together, these results provide a neural framework to explain potential therapeutic effects of brexpiprazole following its long-term administration.

Keywords: Brexpiprazole, Electrophysiological Single Unit Recordings, Serotonin, Dopamine, Norepinephrine
Supported by: Lundbeck/Otsuka

348. Discovery and Development of EMB-001 for the Treatment of Substance Use Disorders

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Background: EMB-001 is a combination of two FDA-approved drugs: metyrapone, a cortisol synthesis inhibitor, and oxazepam, a benzodiazepine. Metyrapone is approved for one day only as a test; oxazepam for various anxiety disorders. We hypothesize that a combination of drugs working by different stress-related mechanisms may reduce substance use disorders, at doses that minimize the risks of each individual drug.
Methods: We summarize preclinical and clinical data supporting the potential utility of EMB-001 for the treatment of substance use disorders.
Results: Metyrapone and oxazepam together reduce cocaine self-administration in rats at doses where each is ineffective alone (Goeders, 2008). A formal dose-finding study confirmed the effective doses in EMB-001 are lower than the effective doses of each drug alone (data not previously disclosed). EMB-001 also reduces nicotine self-administration in rats (Goeders 2012), and attenuates cocaine and methamphetamine cue reactivity in rats (Keller, 2013).
In five trials (O'Dwyer 1995; Murphy 1998; Eriksson, 2001; Jahn, 2004; Rogoz 2004) metyrapone was generally safe and well-tolerated at 500-4000 mg/day for 2-8 weeks. A human study of EMB-001 in cocaine dependence (Kablinger, 2012) showed a significant reduction in cocaine use and was generally safe and well-tolerated.
Conclusions: Preclinical data demonstrate that EMB-001 is effective in several animal models of drug addiction. A human study showed efficacy in cocaine dependence. Future plans include a Phase 1 combined single/multiple ascending dose study to assess safety under GCP conditions, and Phase 2 efficacy studies in cocaine use disorder and/or tobacco use disorder.

Keywords: metyrapone, oxazepam, cocaine, methamphetamine, nicotine
Supported by: Embera NeuroTherapeutics & R01 DA030932

349. Neurophysiological Mechanisms Supporting Flexible, Context Specific, Emotional Regulation

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Background: In everyday life the same stimulus can lead to different rewarding or aversive outcomes depending on the situation. Subjects must therefore recognize a stimulus and the situation, or context, in which it appears to predict outcome accurately and regulate emotions appropriately. Contexts may be defined by abstract factors, like knowledge of a social situation. We sought to identify where and how neural representations of abstract contexts emerge in the brain.
Methods: Two rhesus monkeys performed a task analogous to the Wisconsin Card Sorting Test, switching back and forth several times between two un-cued contexts where different rules must be applied to the same stimuli to maximize reward. During task performance, single neuron activity was recorded simultaneously in the amygdala and prefrontal cortex.
Results: Behavioral evidence indicated that monkeys understood that temporally contiguous events defined each context and therefore the set of rules-in-effect for stimuli. Moreover, all task-relevant variables, including stimulus identity, context, operant action, and expected reinforcement were encoded in each area. The representation of abstract context information was especially strong in the anterior cingulate cortex (ACC), which is prompting us to explore the relationship between ACC and hippocampus while monkeys learn new abstract contexts.
Conclusions: Neural representations of abstract cognitive information are likely important for updating representations of the emotional significance of stimuli. Information about abstract contexts emerges in same neural structures that orchestrate emotions, suggesting that the convergence of cognitive and emotional information in these areas underlies the regulation of emotion.

Keywords: Electrophysiology, Amygdala, Prefrontal cortex, Hippocampus, Emotion
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350. Positive Correlation Between Nightmares and Heart Rate Response to Loud Tones Supports Parasympathetic Dysfunction in Posttraumatic Stress Disorder

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Background: Sleep disruption, including nightmares, is a cardinal feature of posttraumatic stress disorder (PTSD). Relatively little is known about the autonomic basis of sleep pathologies in PTSD.
Methods: Seventy-four adult women with PTSD resulting from either rape or physical assault underwent a loud-tone procedure involving exposure to 10 consecutive, 95-dB, 500-ms, 1000-Hz tones, while skin conductance (SCR) and heart rate (HRR) responses were measured. We hypothesized that SCR, a measures of sympathetic activation, would correlate positively with sleep disruption measured by the Clinician Administered PTSD Scale (CAPS) and Pittsburg Sleep Quality Index (PSQI).
Results: Contrary to prediction, greater SCR to the loud tones correlated with *lesser* sleep difficulties assessed by CAPS ($r=-0.39$, $p=0.004$) and PSQI ($r=-0.31$, $p=0.03$). However, HRR to loud tones correlated positively with CAPS nightmares ($r=0.40$, $p<0.001$), detachment from others ($r=0.32$, $p=0.008$), distressing recollections ($r=0.27$, $p=0.030$), and physiological reactivity on exposure ($r=0.26$, $p=0.0378$), as well as CAPS Total score ($r=0.30$, $p=0.012$). The relationship between HRR and nightmares was robust, because it

remained significant after adjusting for the respective correlations between HRR and other PTSD symptoms (all partial r's ≥ 0.31; p's ≤0.010).
Conclusions: Increased HRR, in the absence of increased SCR, likely reflects reduced parasympathetic tone. Thus, our findings suggest a role for reduced parasympathetic tone in PTSD nightmares. Further research is needed to clarify this relationship.

Keywords: Posttraumatic Stress Disorder, Psychophysiology, Sleep, Nightmares, Heart Rate
Supported by: National Institute of Mental Health, K-23 Career Development Award 1K23MH097844-01A1

351. Short-Latency Afferent Inhibition from the Motor and Dorsolateral Prefrontal Cortex in Healthy Subjects: A Combined TMS-EEG Study

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Background: Short-latency afferent inhibition (SAI) is a transcranial magnetic stimulation (TMS) neurophysiological paradigm that represents an index of central cholinergic activity over the motor cortex (M1). However, SAI effect has not been identified in the prefrontal cortex, especially at the dorsolateral prefrontal cortex (DLPFC), which area is closely related to cognition. We aimed to investigate the SAI effect at the DLPFC in healthy subjects.
Methods: Twelve healthy subjects participated. The combined TMS-electroencephalography (EEG) technique was applied in this study. The median nerve in the right wrist and M1 hot spot was stimulated in M1-SAI paradigm while DLPFC (F5) was stimulated in DLPFC-SAI paradigm. The interstimulus intervals (ISI) of N20 and N20+2 ms were used for the established M1-SAI protocol and a range of ISIs were tested for to explore DLPFC-SAI. Individual N20 latency was determined from somatosensory-evoked potentials (SEP) prior to the SAI procedure.
Results: In M1-SAI there was significant attenuation of the N100-TMS-evoked potential (TEP) amplitude over the midline central (p = 0.002) areas at the ISI of N20+2. Motor-evoked potential (MEP) amplitude and N100-TEP amplitude attenuation were significantly correlated at the midline central area (rho = 0.713, p = 0.009). In DLPFC-SAI the N100-TEP component was also significantly decreased in amplitude at the ISI of N20+4 over the midline central area (p = 0.003).
Conclusions: These findings suggest that cortical activity is modulated in M1 and DLPFC during SAI. The measure of SAI in the DLPFC could potentially enhance our understanding of neurophysiology in healthy and diseased states.

Keywords: short-latency afferent inhibition, dorsolateral prefrontal cortex, combined TMS-EEG study

352. Cortical Excitatory Dysfunction and Depression Severity in Adolescents

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Background: Converging evidence points to the role of glutamate in the pathophysiology of depression. Although adult studies have demonstrated abnormalities in glutamatergic functioning in depression, little prior research has investigated glutamate's role in adolescent depression. Intracortical facilitation (ICF) is an indicator of glutamatergic *N*-methyl-D-aspartate (NMDA) receptor-mediated excitatory neurotransmission that can be examined in vivo using transcranial magnetic stimulation (TMS) techniques. While differences in ICF have been demonstrated between depressed adolescents and healthy controls, no previous studies have examined the relationship between degree of glutamatergic dysfunction and depression severity.
Methods: A sample of 24 depressed adolescents underwent paired-pulse TMS. ICF was recorded with surface electromyography at 10-, 15-, and 20-ms interstimulus intervals. ICF amplitudes were represented as ratios of the resting motor threshold (RMT). Depression severity was assessed with the Quick Inventory of Depressive Symptomatology (QIDS-A_{17}-SR) and the Children's Depression Rating Scale-Revised (CDRS-R). Nonparametric correlational relationships (Spearman's ρ) between ICF and depression severity measures were assessed.
Results: Significant inverse relationships were demonstrated between ICF amplitude at 10 ms and CDRS-R score (left hemisphere: ρ=-0.52, p=0.015; right: ρ=-0.44, p=0.031) as well as QIDS-A_{17}-SR score (left: ρ=-0.46, p=0.035; right nonsignificant). At 15 ms, ICF amplitude had significant negative correlations in both hemispheres for both CDRS-R (left: ρ=-0.63, p=0.002; right: ρ=-0.44, p=0.031) and QIDS-A_{17}-SR (left: ρ=-0.53, p=0.014; right: ρ=-0.41, p=0.045). No significant relationships between depression severity and ICF amplitude at 20 ms were observed.
Conclusions: Our data suggest a relationship between dysfunction in glutamatergic cortical processes and depression severity in an adolescent population.

Keywords: Glutamate, Transcranial Magnetic Stimulation, Intracortical Facilitation, Depression, Adolescent
Supported by: NARSAD Young Investigator Award

353. Childhood Maltreatment, Familial Risk and Childhood Psychopathology: Inflammatory Biomarkers as Mediating Variables

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Background: Parental psychopathology and exposure to childhood maltreatment have been associated with the development of mental disorders. However, the mechanisms underlying this association remain poorly understood. This study aimed to verify the impact of parental psychopathology and reported childhood maltreatment on the levels of neurotrophic, oxidative stress and inflammatory peripheral biomarkers in children.
Methods: This is a cross-sectional, observational study that is part of a large, community, school-based survey. The participants were students with 6 to 14 years of age from public schools in Brazil. A sample of 625 individuals was selected for the blood withdrawal. Clinical assessment included socio-demographic characteristics, psychopathology, parental psychopathology and inquire about childhood maltreatment. Whole blood samples were obtained from all children and peripheral levels of biomarkers were assessed by flow cytometry.
Results: Psychopathology was associated to higher levels of the chemokine CCL-11/Eotaxin-1 and lower levels of soluble tumor necrosis factor receptor II (sTNFRII). Family history of bipolar disorder, unipolar depression and anxiety disorders, as well as exposure to physical abuse and neglect were significantly associated with different levels of inflammatory markers (i.e. interleukin-4, interleukin-10, tumor necrosis factor alpha, CCL-11/Eotaxin-1 and sTNFRII). The inflammatory markers eotaxin and sTNFRII were shown to partially mediate the relationship between risk factors and psychopathology.
Conclusions: Children with a history of parental psychopathology or exposed to childhood maltreatment have a different inflammatory signature, when compared to matched peers. The mediator effect of eotaxin and sTNFRII indicates that inflammatory pathways may underlie the impact of early risk factors on childhood psychopathology.

Keywords: chidlhood psychiatry, family history, childhood maltreatment, inflammation
Supported by: The National Council for Scientific and Technological Development (CNPq), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the São Paulo Research Foundation (FAPESP), Brazil

354. Inflammatory Markers Partially Mediate the Association Between Prenatal Alcohol Exposure and Childhood Psychopathology

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Background: Prenatal alcohol exposure (PAE) has been associated with a wide range of long-term effects. Inflammatory mediators exert a critical role in neurodevelopment and are known to be directly affected by alcohol consumption. This study aimed to explore the relationship between PAE, psychopathology and levels of inflammatory mediators in a large school-based sample of children.
Methods: The study population was composed by 625 students, 6 to 14 years of age. Psychopathology was assessed using the Child Behavior Checklist (CBCL). Prenatal alcohol exposure and associated factors (e.g. parental psychopathology, maternal smoking, obstetric risk factors) were obtained in a household interview with parents. Whole blood samples were obtained and inflammatory markers were measured by flow cytometry. Associations between variables were examined with multivariate analyses of covariance and regression analyses. To test the mediator effects of biomarkers we conducted a multiple mediation analysis.
Results: PAE was significantly associated with higher CBCL scores, as well as with lower levels of interleukin-4 (IL-4) and soluble tumor necrosis factor receptor II (sTNFRII); and higher levels of the chemokine CCL-11/Eotaxin-1. PAE effects were independent of associated factors. Results of mediation analysis showed that CCL-11/Eotaxin-1 and sTNFRII levels partially mediated the relationship between PAE and psychopathology.
Conclusions: PAE is independently associated with higher level of emotional and behavioral problems in children aged 6 to 14, as well as with altered inflammatory biomarkers. Inflammatory markers were shown to partially mediate the relationship between PAE and psychopathology, suggesting that immune-inflammatory processes are critical mechanisms underlying the long-term effects of PAE.

Keywords: childhood psychiatry, prenatal alcohol exposure, inflammation
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355. Differential Effects of Baclofen on Local Fields and Membrane Potential in Response to Steady State Stimulation In Vitro

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Background: Individuals with ASD demonstrate GAMMA (30-50 Hz) band activity perturbations. These alterations have been reversed in-vivo using Baclofen, a recent candidate therapy for ASD. This study explores the effects of baclofen on GAMMA responses in the auditory cortex (ACx) of wild type mice.
Methods: Slices of 3-4 month old C57/BL6 male mice were obtained. Slices were then dyed with voltage sensitive dye and incubated for 2 hours before experimentation. Intact thalamocortical projections leading to ACx were stimulated at 40 Hz (8 stimulations/Gamma-event), and responses recorded via VSDi and LFPs (in layer 2/3). The effect of baclofen (0.10μg/mL; 45 minutes) on this paradigm was then tested. Collected data was analyzed using Igor and the Matlab toolbox Fieldtrip. Once average waveforms of current and membrane-potential were attained, time frequency analysis examined GAMMA responses, with and the integral of the GAMMA recorded. To test the specific hypothesis that baclofen was preferentially affecting later components of the GAMMA responses, GAMMA measures for the second half of the GAMMA response was normalized by the whole GAMMA response.
Results: 40 Hz stimulation produced GAMMA responses in both LFP and VSDi derived data. After application of baclofen, the normalized GAMMA response was increased in VSDi derived data ($p=0.02$), not in local field derived data.
Conclusions: Our results demonstrate the differential affect of GABAB antagonism on current vs. membrane potential derived measures for GAMMA. Therefore, our results suggest that when baclofen recovers proper GAMMA responses in-vivo, its action is presynaptic, since LFP are blind to presynaptic events.

Keywords: ASD, circuit, VSDi, gamma, neurophysiology
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356. Cortical Inhibition in the Pathophysiology and Treatment of Major Depressive Disorder

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Background: Dysfunctional cortical inhibition (CI) has been postulated as a mechanism through which the symptoms of Major Depressive Disorder are mediated. Treatment with electroconvuslive therapy (ECT), the treatment of choice for treatment resistant depression, has previously been associated with enhanced CI. Our objective is to evaluate if the therapeutic mechanisms of ECT response in treatment resistant depression are related to enhanced CI.
Methods: Twenty six patients with treatment resistant depression were enrolled in an acute course of ECT. CI was measured with transcranial magnetic stimulation investigational paradigms known as short-interval cortical inhibition and the cortical silent period, which index GABA-A and GABA-B receptor-mediated inhibitory neurotransmission respectively. CI was measured at two time points: just prior to beginning the acute ECT course and within one week of its termination.
Results: Preliminary analyses of the pre-treatment and post-treatment CI measures showed no aignificant increase in GABA mediated inhibitory neurotransmission after administration of the ECT course. More detailed analyses of the data, including variables such as number and type of ECT treatments, response to treatment, demographics, medications and seizure characteristics during ECT, are necessary.
Conclusions: In contrast to previous smaller scale studies, preliminary analyses of this larger sample did not show increases in neurophysiological measures representing GABAergic cortical inhibition. Further and more detailed analyses are currently underway, as is continued recruitment to expand sample size.

Keywords: Brain Stimulation, Major Depressive Disorder, Cortical Inhibition, Electroconvulsive Therapy, Neurophysiology
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357. Young Girls' Autonomic Responses to Social Stress as a Function of Environmental Adversity and Familial Risk for Depression

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Background: Environmental stress and familial risk are two documented predictors of the development of depression in youth. Psychophysiological measures hold promise in identifying anomalies in youth with environmental (Blair et al., 2013) and familial (Hayden et al., 2014) risk for depression; however, no study has compared the influence of these risk factors on psychophysiological functioning in youth.
Methods: We examined psychophysiological functioning in three groups of girls ages 10-13 years whom we recruited along specific dimensions: high early life stress (High Stress), low early life stress (Low Stress), and a mother with recurrent depression (Maternal Depression). Specifically, we assessed girls' parasympathetic responses (respiratory sinus arrhythmia [RSA]) at baseline and as they completed a standardized social stress task.
Results: As hypothesized, both the High Stress and Maternal Depression groups exhibited lower baseline RSA than did the Low Stress group, did not differ significantly from each other; the Maternal Depression group exhibited lowest baseline RSA ($p=0.03$). These group differences in baseline RSA were maintained throughout the stressor. Contrary to predictions, the groups did not differ in acute RSA reactivity to or recovery from the stress task (all $ps>0.27$).
Conclusions: Comparably low baseline RSA as a function of environmental and familial risk for depression suggests that these factors contribute at an equivalent level to allostatic load (McEwen, 2000) as one psychophysiological pathway that has been implicated in emotion dysregulation. In our follow-up longitudinal research, we aim to link this autonomic dysfunction to the subsequent onset of depression in at-risk youth.

Keywords: Respiratory Sinus Arrhythmia, Depression, At-Risk Youth, Trier Social Stress Test, Parasympathetic Arousal
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358. Increased Cortical Excitability in Major Depressive Disorder Identified Using Deep Transcranial Magnetic Stimulation

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Background: Motor threshold (MT, the minimum intensity of motor cortical stimulation needed to evoke movement) provides a quantifiable noninvasive measure of neural excitability. Motor threshold is measured to adjust for variable sensitivity to deep transcranial magnetic stimulation (dTMS), an effective, noninvasive, neuromodulatory depression treatment. Abnormalities in MT have been reported in psychiatric disorders but, to our knowledge, MT differences assessed with dTMS have not been previously reported. We examined MTs of patients with major depressive disorder (MDD) and healthy controls (HCs).
Methods: Data were pooled from dTMS studies, including three groups: unmedicated MDD (n=76), medicated MDD (n=34), and HCs (n=32). Group differences in MT were compared using single factor ANOVA; post hoc Tukey's HSD tests were used to examine specific comparisons. Gender was similar between groups, though age differed. Multiple regression was used to control for age.
Results: There was a significant difference in MT between groups ($F=7.18$, $MSE=83.02$, $p=0.001$). Post-hoc analysis revealed that MT (mean ± standard deviation) was lower in unmedicated MDD (53.5 ± 9.3) compared to HC (59.8 ± 7.5) at a 0.05 level of significance. There was no significant difference in MT between medicated MDD (58.4 ± 8.5) and HC. This effect remained significant when controlling for age ($R2=0.118$, $\beta=-3.92$, $p=0.0001$).
Conclusions: While MT in unmedicated MDD was significantly lower than HC, this difference was not seen in medicated MDD. Causality cannot be inferred, but these preliminary results suggest increased cortical excitability in MDD, which could reflect glutamatergic or GABAergic dysfunction.

Keywords: Cortical, Excitability, TMS, MDD, Motor Threshold
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359. Lipid Abnormalities are Associated with Mood Symptoms in Adolescents with Bipolar Disorder

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Background: Abnormal lipid (low-density lipoprotein (LDL); high-density lipoprotein (HDL); triglycerides (TG); total cholesterol (TC)) levels are common in bipolar disorder (BD). High lipid levels may confer risk for atherosclerosis and have also been linked with severity of mood symptoms. Given the paucity of data on this topic, we examined the association between lipids and mood symptoms in BD adolescents.
Methods: Thirty BD adolescents (ages 13-20) and 25 controls (ages 13-19) were interviewed using extended depression and mania sections of the Schedule for Affective Disorders and Schizophrenia for School Age Children. Levels of LDL, HDL, TG and TC were obtained and analyzed dimensionally using International Diabetes Federation cut-offs. Mann-Whitney U-tests and Spearman correlations were performed using SPSS 22.
Results: BD adolescents with at least one lipid abnormality had significantly greater current depression scores (20.47±10.36) compared to adolescents without lipid abnormalities (10.46±6.93) ($U=41.00$, $p=0.008$). In BD adolescents, current depression scores were significantly correlated with LDL ($\rho=0.748$, $p<0.001$), TG ($\rho=0.442$, $p=0.019$), TC ($\rho=0.651$, $p<0.001$), but not HDL ($\rho=0.107$, $p=0.588$). LDL, TG and TC findings remain significant after controlling for second-generation antipsychotics ($p<0.001$, $p=0.026$, $p<0.001$, respectively). Most severe past depression episode scores were significantly correlated with TG only ($\rho=0.374$, $p=0.050$). No significant correlations were found between lipid levels and hypomanic symptoms. Compared to the control group, TG levels were higher in BD adolescents ($p=0.020$).
Conclusions: Lipids are associated with depression symptoms among BD adolescents. Larger studies looking at these associations prospectively and examining the effect on mood of pharmacologically altering lipid levels are warranted.

Keywords: bipolar disorder, mood symptoms, lipid abnormalities, adolescents
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360. State and Trait Markers, Not Clinical Diagnoses are Associated with Brain SNAP-25 Isoform Pattern of Expression, a Translational Approach

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Background: Evidence suggests that bipolar disorder (BP) and schizophrenia share some common biological processes and symptoms; however, little is known about the underlying molecular biology. One candidate for this shared pathology is SNAP-25, a neurotransmitter vesicular docking protein that is developmentally regulated and differentially expressed across the brain. This range of expression potentially makes SNAP-25 a key site of pathophysiology. In this project, we examined whether the SNAP-25 isoforms are differentially expressed for both state and trait characteristics in postmortem brain tissue of subjects with BP, schizophrenia and normal controls.
Methods: SNAP-25a and b isoform protein and mRNA were measured in postmortem Brodmann's area (BA)9 and BA24 from subjects with BP (n=9), schizophrenia (n=7) and normal controls (n=12). Demographic, clinical variables including emotional levels in the last week of life, and lifetime impulsiveness were acquired. This information was obtained by next of kin interviews and review of medical records.
Results: We did not any SNAP-25 mRNA or protein level changes associated with clinical diagnosis. Rather we found that the level SNAP-25 isoforms, BA9/BA24 ratio and the b/a isoform ratios were different based on ethnicity, end of life emotional state (irritableness, anxiety and psychosis), and smoking. Those who had a diagnosis of alcohol use disorder (AUD) had a lower level of SNAP-25b protein in BA24 compared to those without AUD.

Conclusions: This data suggests that SNAP-25 mRNA and protein expression has both trait and state dependent aspects which are not related to clinical diagnosis.

Keywords: postmortem, SNAP-25, bipoalr disorder, schizophrenia, Endophenotype
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LATE BREAKING
Late Breaking Poster Session

Thursday, May 14, 2015 – 5:00 PM – 7:00 PM
Concert Hall – Convention Floor

The Late Breaking poster abstracts (No. 361 through 399) were accepted after this supplement was published. See the On-Line Program Planner or Mobile App for the complete abstract.